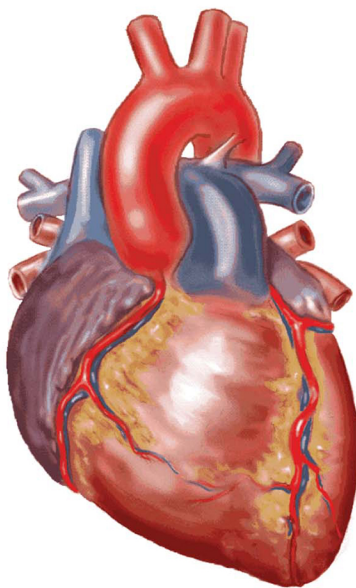


Sudden Cardiac Death

Predictors, Prevalence
and Clinical Perspectives

Cardiology Research and
Clinical Developments



Ivana Vranic
Editor

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SUDDEN CARDIAC DEATH

PREDICTORS, PREVALENCE

AND CLINICAL PERSPECTIVES

IVANA VRANIC
EDITOR



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PREFACE

In front of you, there is a top clinical compilation on sudden cardiac death causes. From the various geographical regions in the world comes different clinical perspective to the SCD problem and sheds the light on predictors and estimated prevalence in genetic inheritance worldwide.

Hopefully, this is just a solid beginning for an interested reader to continue expand research in everyday clinical practice.

In the first section of this book, genetic basis for various channelopathies is discussed. Here, we may read about inherited arrhythmia syndromes and cardiac channelopathies known to have genetic mutations in the genes that encode for cardiac ionic channels which can disrupt the balance of ionic currents of the action potential leading to an unusual electrocardiographic phenotype. The field of cardiac channelopathy is rapidly expanding with increasing discovery of new genes associated with cardiac arrhythmias including long QT syndrome, Brugada syndrome, short QT syndrome and Catecholaminergic polymorphic ventricular tachycardia. Heterogeneity exists in disease manifestation in patients carrying the same mutation. Diagnosis of affected individuals with timely and appropriate therapy can prevent dramatic events. The identification of genes underlying these diseases has enabled identification of asymptomatic individuals at risk of sudden cardiac death carry the genetic mutation responsible for the disease. For this reason, genetics has been incorporated into clinical guidelines of sudden cardiac death. This chapter will briefly review of the genetic basis, pathophysiology, risk stratification and the management approach of this group of syndromes.

Also, it is our knowledge that notable number of prominent sport professionals die during or short after sport activity from unknown reasons. These cases are associated with unexpected ventricular fibrillation and sudden cardiac death in young individuals with normal heart.

The chapter two will provide a historical summary of the evolution of the concept of early repolarization from its original description to the latest works and a guide to help physicians in evaluating individuals with this common electrocardiographic pattern.

It is known that for more than 70 years, early repolarization has been considered to be a common normal variant. In the general population, the prevalence ranges between 5 and 13%, and in athletes, a rising trend is observed from 20 to 90%. Nevertheless, from the latter half of the 1990s, a growing number of case reports, series, observational and retrospective studies reported that the presence of various electrocardiographic patterns attributed to early repolarization may constitute a potential marker for the increased risk of sudden death in otherwise normal individuals, casting a dark shadow on this ECG peculiarity.

For many centuries, mysterious death of prominent professional sportsmen, have preoccupied media and doctor's attention, especially because deceased athletes previously had achieved extraordinary sports results without having heart problems. It is not easy to determine the accurate epidemiology of SCD in sport. Much depends on the selected inclusion criteria for the analysis, the age of the athletes, the level of athletic achievement, sporting experience, type of sport, and other factors.

Chapter three deals with epidemiology of SCD in Sport and cardiac arrest during physical activity, reporting also mass media information that recorded 1,866 cases of sudden death and cases of nonfatal which were observed in 38 sports. The SCD incidence rate demonstrated a statistically significant increase by 6% annually. Also, the data on the sports epidemiology connected to SCD are quite various, depending on national sporting traditions, age, gender, and group inclusion criteria (professional sports, school sports, general fitness activity). In some cases, it was possible to obtain the medical histories of the victims or data on the presence of some specific diseases or conditions or potential symptoms preceding the fatal episode. This suggests that even minor, non-specific health complaints in regularly training athletes must be taken seriously by doctors, coaches, and the athletes themselves, as they may herald the onset of a life-threatening event. Some conditions in athletes, often considered to be undoubtedly life-threatening, such as syncope, to the contrary, are not always associated with a risk of sudden death, although that risk should always be ruled out first.

Chapter four deals with screening challenges in sportsmen and it's practical clinical value. Various hemodynamic and electrophysiological factors respond significantly to exercise in a healthy heart. Some of the physiological changes in response to acute high-intensity aerobic exercise include substantial increases in skeletal muscle oxygen consumption and cardiac output. The news of sudden cardiac death (SCD) of anyone, anywhere on the planet is indeed tragic, and it could leave complex social and psychological consequences, particularly when this unexpected event occurs in the total absence of any symptom and warning beforehand. Nevertheless, there is a common contention among most people that athletes are symbols of health and strength. However,

the tragic incidence of SCD in young athletes nullifies this fact and generates widespread public and media attention accordingly. Its incidence rate is higher for athletes in comparison with non-athlete counterparts. Thus, the SCD in athletes as a major global health problem requires scholarly attention and scientific scrutiny.

Chapter five discusses the present knowledge on epidemiology and physiology of malignant ventricular tachyarrhythmias in patients with congenital heart disease (CHD) and the data on clinical timeline of ventricular tachyarrhythmia in a large cohort of patients with a variety of congenital heart defects. Noteworthy, many various rare inherited syndromes that are associated with CHD are at focus, and interrelationship between ventricular premature beats, (non)-sustained ventricular tachycardias and ventricular fibrillation are being discussed. Here it is shown how ventricular tachyarrhythmias appear on average at the age of 40 years, and how rare they develop in patients with only non-sustained ventricular tachycardias.

Adult patients with congenital heart disease are at risk of sudden cardiac death caused by malignant ventricular tachyarrhythmias. The reported prevalence of ventricular tachyarrhythmias is up to 30% and they are mainly reported in patients with tetralogy of Fallot and transposition of the great arteries. These dysrhythmias may be preceded by non-sustained ventricular tachycardia. At this moment, 90% of CHD patients is expected to survive into adulthood in high income countries. The improvements in healthcare have significantly increased the life expectancy of CHD patients. Yet, it also has a flipside: the aging and growing population of CHD patients often undergoes multiple surgical procedures throughout life, needs long-term expert medical care and has an increased risk of arrhythmias and SCD.

Chapter six gives new insights into less frequently observed problem women and SCD. This Chapter reviews the etiology underlying SCD in women and summarizes the major risk factors for SCD as a guideline to determine the high-risk patients for preventive treatment. Prediction and prevention of SCD is an area of active investigation but current guidelines state that women have a lower incidence of sudden coronary death compared to men. In two thirds of women who died suddenly, sudden cardiac death was the first clinical manifestation of coronary heart disease. Post-menopausal women have the greatest population burden of cardiovascular disease including SCD. The etiology of SCD in women is less clear, because women are underrepresented in studies of SCD and experience fewer SCD events than men. Several studies suggest that pre-existing coronary disease is less predictive in women, and other etiologies are more likely. Also, women with SCD are less likely to have underlying coronary artery disease (CAD) than men that makes necessary to identify risk factors other than CAD or systolic dysfunction. Heart failure with preserved left ventricular systolic function, increased sympathetic excitability which may be assessed by meta-iodo-benzyl-guanidine uptake, depression, and/or use of antidepressants are common risk factors of SCD in women.

Chapter seven deals with prevalence on the SCD and hypertrophic cardiomyopathy, and accurate risk estimation that can be extremely challenging. That recently became a source of argument between European and American experts. Although the main risk factor of SCD is definitely a previous resuscitated cardiac arrest, the identification of individuals at high risk of SCD in primary prevention is still a debated issue.

Over the last few years, cardiovascular research is going very fast in discovering new modifying risk factors. Thus, LV apical aneurysm, multiple sarcomere gene mutations, myocardial fibrosis (MF) and End-Stage (ES) HCM are becoming more and more important as final arbitrators especially in cases at intermediate risk. The need of an international agreement is a compelling issue that can't be further postponed.

Chapter eight discusses about new insights in Chagas disease which has been a major cause of death in Latin American countries and it is becoming a real problem in public health. In the Hispanic population common causes of SCD include coronary artery disease (CAD), Chagas disease and idiopathic dilated cardiomyopathy. After a century since the description of the disease, Chagas still represents a major public health challenge in Latin America. In the last decades, several interventions encompassing the primary, secondary, and tertiary prevention levels of Chagas disease have been attempted. The control of both vector and blood transfusion-based transmission of *T. cruzi* (primary prevention) has been successful in many endemic regions, but early detection and etiological treatment of asymptomatic subjects have been largely underutilized.

Sudden cardiac death is the most common cause of death in Chagas disease (55%-65%), followed by congestive heart failure in 25% - 30% and cerebral or pulmonary embolism in 10%-15%. Most SCD cases occur in patients with manifest chagasic cardiomyopathy between 30 to 50 years old. 20% of patients that died suddenly do not report previous symptoms. SCD in chagasic patients is generally related to arrhythmias, and less common to thromboembolic events (massive pulmonary or cerebral embolism) or rarely a rupture of a LV aneurysm. Ventricular fibrillation has been reported to be the major cause of death of SCD. The risk of sudden cardiac death is not the same in all patients with chronic Chagas disease and this is why several authors have tried to identify predictor factors. A scoring system would be essential for establishing effective prevention strategies. The patients identified as high-risk of death can get a benefit from aggressive therapy, including electrophysiological studies using an implantable cardioverter.

Chapter nine deals with new and emerging technologies to detect SCD risk. Among the emerging imaging modalities proposed for the study of structural heart diseases, CMR imaging plays an important role for IHD diagnosis, diagnostic and prognostic evaluation of SCD survivors and families of SCD victims. CMR allows distinction between acute and chronic IHD through the assessment of myocardial edema by T2-

weighted sequences, identification of myocardial fibrosis by T1-mapping analysis and ECV calculation, and assessment of the infarcted area by LGE imaging.

A number of studies aimed to explore of the incremental prognostic value of myocardial scar quantification highlighted the importance of “gray zones” – regions of intermediate contrast enhancement likely representing potentially arrhythmogenic zones of viable and non viable myocardium - which has been shown to be a strong independent predictor of VT inducibility, appropriate ICD therapy and mortality. Reduced LVEF is the main criteria underlying current indications for ICD implantation for primary prevention of SCD. However, any strategy for primary prevention based on LVEF alone has major limitations.

LGE is a well-established technique, offering better discriminative accuracy of LGE than LVEF for individual arrhythmic risk stratification and a possible solution to unmet clinical needs.

Chapter ten is about rare and scarce insights about cardio-oncology. Patients who survive their cancer are reaching now to a survival rate of up to 90% in some cancers like Breast cancer, and they were given either the classical chemotherapy like anthracyclines or the new targeted therapies like VEGF inhibitors or other forms including Radiotherapy and are facing a new threat to their lives caused by the damaging insult which was put on them by these therapies leading to the development of various cardiovascular pathologies that are making a new challenge of survival and one of the important threats is the development of the catastrophe of sudden cardiac death, which is our main concern in this chapter.

Irradiation of the heart to a sufficiently high dose can damage any component of the heart, including pericardium, myocardium, heart valves, coronary arteries, capillaries, and the conducting system. For instance acute pericarditis can take place rapidly in the course of the radiotherapy to the chest. This can lead to pericardial effusion, tamponade and pericardial fibrosis (Echocardiography changes) and lead to a haemodynamic compromise that may initiate a sudden cardiac death. Cancer patients have 2-3 fold liability for thrombosis than the non-cancer patients and highest with metastatic lesions and /or established risk factors and usually the affected patients have poor prognosis. Massive PE in cancer patient is not infrequently under diagnosed. Proper cardio-toxicity management will allow us to continue the cancer treatment and at the same time prevent or reduce the cardio-toxicity and this should result in higher, safer and prolonged survival rate.

Chapter eleven is dealing with the latest ESC 2015 Guidelines recommendation to implant an ICD in patients with symptomatic heart failure (NYHA Class II-III) and a $LVEF \leq 35$ in patients as an optimal medical therapy for at least 1 month, with a Class I indication, level of evidence A for ischemic (at least 60 days after a myocardial infarction) and B for non ischemic patients. Without doubt echocardiography is the most highly available imaging modality for SCD risk stratification, significant progress has

been achieved over the traditional approach in which two-dimensional (2D) LVEF is applied for this purpose. Among the most notable developments three-dimensional echocardiography and myocardial strain imaging are worth noting and might inexpensively improve our current risk stratification process. Recently strain, which reflects the change of length or thickness of myocardial fibers, has been incorporated into routine clinical practice. Strain measured with speckle tracking echocardiography, is based on the presence of natural acoustic markers in ultrasound images, working as a fingerprint for each myocardial segment that can be followed over the cardiac cycle and allow to describe deformation. All clinical conditions that are known to have direct link to SCD are discussed here with new insights in everyday clinical practice.

In the end, I would like to express my personal gratitude for all the effort implied in this Book to fulfil the highest demands put into this project of SCD riddle solving in different research modalities. Also, I would recommend this Book as a milestone for further research in SCD phenomenon.

Ivana Vranic, MD, PhD, FESC

Chapter 1

ARRHYTHMOGENIC SYNDROMES ASSOCIATED WITH SUDDEN CARDIAC DEATH

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ABSTRACT

Sudden death (SD) is defined as an unpredicted natural decease of a healthy individual. The main cause of SD is cardiac alterations, and then called sudden cardiac death (SCD). Recent advances in cardiology have developed new guidelines in diagnosis, treatment as well as prevention of diseases associated with SCD. Despite this fact, early identification of individuals at risk remains as one of the main current challenges for cardiologist. A major cause of SCD is congenital alterations and structural heart diseases although a significant number do not show any heart defect during autopsy. In these unresolved cases, channelopathies are considered the first potential cause of SD. Due to all these diseases are of genetic origin, family members could be at risk, despite asymptomatic. Unfortunately, SCD is usually the first and only clinical manifestation of an inherited cardiac disease that had remained undetected by conventional clinical investigations. In several cases, physical activity can be the trigger for SCD as first symptom. Recent technological advances in genetics have improved the use of genetic test into SCD field. It may helps to identify the cause of death in affected patients, in post-mortem cases without conclusive diagnosis as well as asymptomatic family

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members at risk. Our chapter focuses on recent advances on arrhythmogenic disorders associated with SCD.

INTRODUCTION

Sudden death (SD) is defined as an unexpected and natural event that occurs within the first hour after onset of symptoms in a healthy individual, and in which a thorough autopsy fails to demonstrate a cause of death (Basso et al., 2010). It represents therefore a tremendous burden to families, community and health care, especially when occurs in paediatric population. Cardiac alterations are the main cause of SD (sudden cardiac death -SCD-). In population >50 years old, nearly 80% of SCD cases are consequence of coronary heart disease, while in population <35 years old, SCD is mainly due to inherited genetic variations (Oliva et al., 2010). Given its genetic nature, there are important implications for family members. Therefore, the genetic testing has the goal to increase diagnostic yield, facilitating the cascade genetic screening of family members with more focused testing (Campuzano et al., 2014b). One major inconvenient in clinical diagnose of families is incomplete penetrance and variable expressivity, impeding identify all relatives at risk of SCD (Giudicessi and Ackerman, 2013). In several cases, physical activity can be the trigger for SCD as first symptom. Focusing on inherited syndromes, two main groups have been proposed: channelopathies, in which the arrhythmogenic substrate is found in the abnormality of the electrical properties of the heart without any structural defect, and cardiomyopathies, in which arrhythmias are related to the presence of structural heart alterations (Wellens et al., 2014). Genetic research has shown that SCD-associated inherited syndromes are caused by pathogenic alterations in genes encoding four types of myocyte proteins: sarcomeric, cytoskeletal, desmosomal, and ion channels or associated proteins. While the mechanistic substrate is different in both groups, the end point is a common feature (Campuzano et al., 2014a). In this chapter we will focus on genetic basis of arrhythmogenic disorders associated with SCD.

CHANNELOPATHIES

As mentioned before, the term “channelopathies” refers to cardiac disease characterized by structural normal heart leading to arrhythmogenesis, syncope and SCD (Martin et al., 2013). These arrhythmogenic diseases are induced by pathogenic variants mainly in genes encoding cardiac ion channels (mainly sodium, potassium and calcium), or associated proteins. In general, depending on which ion channel is affected, different syndromes will be present. Nevertheless, the same syndrome may show a certain degree of overlap if different types of channel can be affected.

Table 1. Genes associated with channelopathies

Chanel	Disease	Inheritance	GENE (ID)
Sodium	LQT	Autosomal Dominant	<i>SCN5A</i> (6331) <i>SCN4B</i> (6330) <i>SCN1B</i> (6324)
	BrS	Autosomal Dominant	<i>SCN5A</i> (6331) <i>GPD1L</i> (23171) <i>SCN1B</i> (6324) <i>SCN3B</i> (55800) <i>SCN2B</i> (6327) <i>SCN10A</i> (6336)
Sodium-Associated	LQT	Autosomal Dominant	<i>CAV3</i> (859) <i>SNTA1</i> (6640)
	BrS	Autosomal Dominant	<i>RANGRF</i> (29098) <i>SLMAP</i> (7871) <i>PKP2</i> (5318)
Potassium	LQT	Autosomal Dominant	<i>KCNQ1</i> (3784) <i>KCNH2</i> (3757) <i>KCNE1</i> (3753) <i>KCNE2</i> (9992) <i>KCNJ5</i> (3762) <i>KCNJ2</i> (3759)
		Autosomal Recessive	<i>KCNQ1</i> (3784) <i>KCNE1</i> (3753)
	SQT	Autosomal Dominant	<i>KCNH2</i> (3757) <i>KCNQ1</i> (3784) <i>KCNJ2</i> (3759)
	BrS	Autosomal Dominant	<i>ABCC9</i> (10060) <i>KCNE3</i> (10008) <i>KCNJ8</i> (3764) <i>HCN4</i> (10021) <i>KCND3</i> (3752)
		X-linked Dominant	<i>KCNE5</i> (23630)
	CPVT	Autosomal Dominant	<i>KCNJ2</i> (3759)
Potassium-Associated	LQT	Autosomal Dominant	<i>AKAP9</i> (10142)
Calcium	BrS	Autosomal Dominant	<i>CACNA1C</i> (775) <i>CACNB2</i> (785) <i>CACNA2D1</i> (781) <i>TRPM4</i> (54795)

Table 1. (Continued)

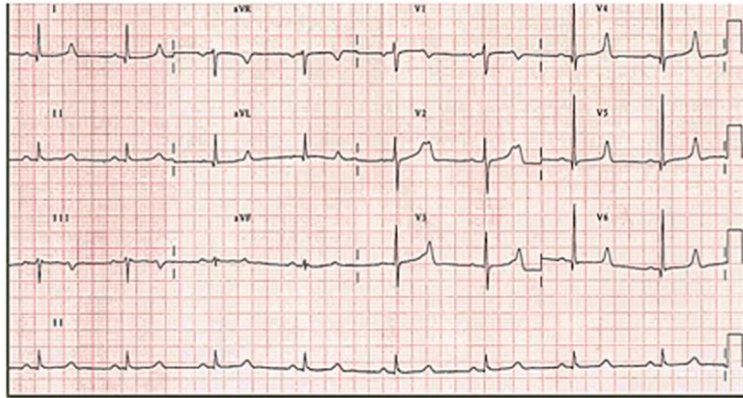
Chanel	Disease	Inheritance	GENE (ID)
	SQT	Autosomal Dominant	<i>CACNA2D1</i> (781)
	LQT	Autosomal Dominant	<i>CACNA1C</i> (775)
			<i>RYR2</i> (6262)
			<i>CALM1</i> (801)
	CPVT	Autosomal Dominant	<i>RYR2</i> (6262)
		Autosomal Recessive	<i>CASQ2</i> (845)
Calcium-Associated	LQT	Autosomal Dominant	<i>ANK2</i> (284)
		Autosomal Recessive	<i>TRDN</i> (10345)
	CPVT	Autosomal Dominant	<i>CALM1</i> (801)
		Autosomal Dominant	<i>CALM2</i> (805)
		Autosomal Recessive	<i>TRDN</i> (10345)

BrS Brugada syndrome, CPVT Catecholaminergic polymorphic ventricular tachycardia, LQTS Long QT syndrome, and SQTS Short QT syndrome.

In addition, it is well-known the interaction of genetic and environment as a phenotype modifier (Campuzano et al., 2010). Ion channels are glycoproteins embedded in the membrane of the myocytes which allow flux of ions in and out of the cell to modulate the electrical gradient. The flow of ions moves charge and induce the formation of cardiac action potential (electric current), which is regulated by synchronized opening and closing of the channels following a voltage gradient. These diseases usually affect the electrical generation and transmission through myocytes, a critical step in the myocardial electromechanical activity, which requires the coordination of several elements, including ion channels and structural proteins, named ion channel macromolecular complexes (Martin et al., 2013). The complexity of this process remains a major limitation for understanding arrhythmogenic mechanisms. Currently, the main channelopathies are: Brugada syndrome (BrS), long QT syndrome (LQTS), short QT syndrome (SQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) (Priori and Blomstrom-Lundqvist, 2015). We will focus on these four arrhythmogenic syndromes.

Brugada Syndrome

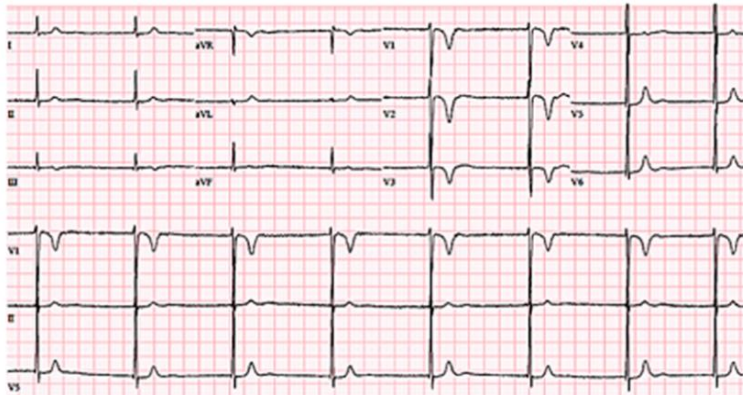
The Brugada syndrome (BrS) is a rare entity characterized by a coved-type ST-segment elevation in atypical right-bundle branch block in leads V1 to V3 of ECG, without structural heart disease (Brugada and Brugada, 1992). The ECG pattern can be baseline or intermittent, and it can be unmasked during a drug test (class IC sodium



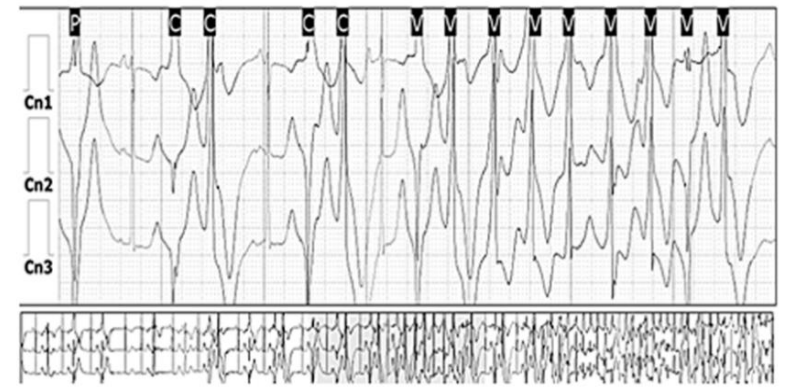
A



B



C



D

Figure 1. Electrocardiograms showing A. Long QT Syndrome B. Brugada Syndrome C. Short QT Syndrome, and D. Catecholaminergic Polymorphic Ventricular Tachycardia.

channel-blockers). The prevalence has been estimated in 3-5 per 10000 people yearly, and the average age of onset of events is about 40 years old, being men gender the main affected (75%). SCD related to BrS typically occurs during sleep, at rest or upon increased vagal tone (Brugada et al., 2014). Patients with BrS usually remain asymptomatic and modulating factors such as fever, exercise or drugs (www.brugadadrugs.org), may play a major role in the dynamic nature of the ECG. Even though SCD in this syndrome is uncommon during exercise, the Recommendations for Competitive Athletes with Cardiovascular Abnormalities recommend that BrS patients should avoid high-intensity exercise. The management of patients diagnosed with BrS is difficult because of lack of effective medical therapy to prevent arrhythmias. Thus, the schemes for risk stratification are quite limited because little is known about the clinical presentation and prognosis. In patients showing diagnosed BrS and history of syncope, aborted SD, nocturnal agonal breathing or seizures, are considered as a subgroup of patients at higher risk SCD, and ICD implantation is indicated. Currently, the ICD is the best preventive measure in BrS. However, ICD implantation in symptomatic is not free from controversy, especially in children (Sarquella-Brugada et al., 2016). The decision to implant an ICD in a child is not an easy task as this is a life-long therapy, not free from complications.

There is limited data proving the benefit of other preventive therapies but if patients also show arrhythmias, Quinidine could be indicated. BrS can associate AV conduction disturbances and supraventricular tachycardia, so we question the presence of palpitations and eventually treat these arrhythmias with ablation (Arbelo and Brugada, 2014).

Concerning genetic bases, more than 250 pathogenic variants have been identified in 19 genes, so far (*ABCC9*, *CACNA1C*, *CACNA2D1*, *CACNB2b*, *GPD1-L*, *HCN4*, *KCND3*, *KCNE3*, *KCNE5*, *KCNJ8*, *PKP2*, *RANGRF*, *SCN10A*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN5A*, *SLMAP*, and *TRPM4*) (Sarquella-Brugada et al., 2016). A comprehensive genetic analysis only identifies the pathogenic cause in 35%-40% of families, and approximately 25%-30% of all these genetically positive patients carry a pathogenic variant in *SCN5A* (BrS type 1). Hence, current guidelines only recommend genetic analysis of this gene (Priori et al., 2015). The *SCN5A* gene encodes the cardiac sodium channel Nav1.5 and pathogenic variations induce a loss of function (Chen et al., 1998). Other pathogenic variations have been published in beta subunits that modify Nav1.5 (increasing or decreasing INa) and encoded by *SCN1B*, *SCN2B*, and *SCN3B* (Hu et al., 2009; Riuro et al., 2013; Watanabe et al., 2008). Recently, it has been published implication of *SCN10A*, a neuronal sodium channel gene encoding Nav1.8 which modulates Nav1.5 expression (Bezzina et al., 2013), but several studies should be performed to clarify the role of this gene in BrS. In addition, pathogenic variants in the *GPD1-L* gene reduce both the surface membrane expression and the inward sodium current (London et al., 2007). Recently, the *RANGRF* gene (MOG1 protein) has been reported that impair the trafficking of Nav1.5 to the membrane (Kattygnarath et al., 2011). In 2012, a pathogenic variant was identified in

SLMAP, a gene which encodes the sarcolemmal membrane-associated protein, localized at T-tubules and sarcoplasmic reticulum and that modulates intracellular trafficking of hNav1.5 channel (Ishikawa et al., 2012). Recently, it has been also reported pathogenic variants in *PKP2* (plakophilin-2 protein). This is a desmosomal gene and correlation between the loss of expression of plakophilin-2 and reduced Ina (Cerrone and Delmar, 2014; Cerrone et al., 2014). Regarding potassium channels, the first evidence implicating novel gain-of-function pathogenic variant in *KCND3* associated with BrS was published in 2011 (Giudicessi et al., 2011). This gene encodes a member of the potassium channel, voltage-gated, and is prominent in the repolarization phase of the action potential. Other genetic alterations have been reported in the *KCNE3* gene (MiRPS2 protein) which encodes a regulatory β subunit of the transient outward potassium channel Ito (Delpon et al., 2008). Despite BrS follow mainly an autosomal dominant pattern of inheritance, one pathogenic variant associated with BrS has been located in the *KCNE1L* gene (*KCNE5*) - X-linked- (Ohno et al., 2011). Recently, a BrS family carrying a pathogenic variant in the *KCNJ8* gene has been also reported (Medeiros-Domingo et al., 2010). In addition, BrS was also associated with *HCN4* which encodes hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 (Ueda et al., 2009). It is expressed in sinus node and cells of cardiac conduction system, and loss of function of this protein is associated with sinus nodal dysfunction. The *ABCC9* gene encodes the sulfonylurea receptor subunits SUR2A. Pathogenic variants in this gene induce a gain-of-function in I (K-ATP) when coupled with a loss-of-function in *SCN5A*, and may underlie severe arrhythmic phenotype (Hu et al., 2014). Finally, genetic alterations in calcium channels or associated proteins have been also reported in BrS families. Genetic variants in *CACNA1C* are responsible for a defective α_1 unit of the type-L calcium channels. It induces a loss of channel function, but linked to shorter QT interval (Antzelevitch et al., 2007). Other genetic variants in *CACNB2b* lead to the same ECG traces showing combination of BrS and shorter QT interval (Antzelevitch et al., 2007). In 2010, the *CACNA2D1* gene was associated with BrS (Burashnikov et al., 2010). Finally, pathogenic genetic variants in the *TRPM4* gene have also been reported. This gene encodes the transient receptor potential melastatin protein number 4, a calcium-activated nonselective cation channel, and member of a large family of transient receptor potential genes (Stallmeyer et al., 2012).

Long QT Syndrome

Long QT syndrome (LQTS) is a rare heterogeneous cardiac channelopathy characterized by QT interval prolongation in the ECG (QTc > 460 ms women and >450 ms men) (Amin et al., 2013). The spectrum of ECG abnormalities inducing electrical instability includes notched or biphasic T waves and T wave alternant. The LQTS presentation varies from asymptomatic patients to episodes of syncope due to ventricular

tachyarrhythmia (*Torsade de Pointes*) in the setting of a structurally normal heart. LQTS has a prevalence of 1/2500 individuals, being a major cause of SCD among young people (Mizusawa et al., 2014). In all patients, beta-blocker administration at high doses is highly recommended because it decreases the risk of SCD although do not provide full protection. The dose is adjusted according to the medical tolerance to these drugs (www.torsades.org). However, controversy exists regarding the efficacy of cardioselective beta-blockers, such as atenolol. ICD implantation is mandatory for those patients having had an aborted SCD and for those at risk of fatal arrhythmias (Behere et al., 2014). LQTS can be congenital or acquired, the last one generally associated with drugs and electrolyte imbalance (hypokalemia, hypocalcaemia and hypomagnesaemia). The congenital form is associated with pathogenic alterations in ion channels and/or associated proteins.

Regarding genetics, LQTS can follow an autosomal dominant or recessive pattern of inheritance. Currently, more than 1000 pathogenic variants have been identified in 18 genes (*AKAP9*, *ANK2*, *CACNA1C*, *CALM1*, *CALM2*, *CAV3*, *KCNE1*, *KCNE2*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNQ1*, *RYR2*, *SCN1B*, *SCN4B*, *SCN5A*, *SNTA1*, and *TRDN*). All these genes together are responsible for 80%–85% of all LQT cases (Nakano and Shimizu, 2016). Recently, intragenic rearrangements (large deletions and duplications) have been associated with LQTS, suggesting that the cause of disease could be due to copy number variants (CNVs) affecting any of these 18 genes. Detection rate for CNVs among LQTS families seem to be around 2%-11%. Major genes associated with LQTS are *KCNQ1* -type 1- (30%-35%), *KCNH2* -type 2- (25%-30%) and *SCN5A* type 3- (5%-10%) which are responsible for 65%-75% of all LQTS cases. Recent guidelines recommend only testing these 3 main genes in families diagnosed of LQTS, especially if there is SCD of a young family member (Priori et al., 2015). Pathogenic variants in the *KCNQ1* gene are main responsible for prolonged QT interval. This protein binds to the protein encoded by the *KCNE1* gene (minK) to form the I_{ks} functional complex (Bianchi et al., 1999). Pathogenic variants in *SCN5A* causes a functional defect based on incomplete inactivation of the channel, thereby allowing continued entry of sodium ions into the cell during repolarization and leading to enhanced function. Another disease-associated gene is *KCNH2* which encodes the alpha subunit of the I_{kr} complex (Sanguinetti et al., 1996); the alpha subunit is determined by the *KCNE2* gene. This I_{kr} complex is the most important inducer of fast repolarization in phase 3. Pathogenic variants in *KCNH2* lead to loss of function in the I_{kr} channel, and account for 35% to 45% of LQT syndrome cases. In *KCNE2*, the pathogenic variants also lead to loss of channel function. Another gene implicated in long QT syndrome is *KCNJ2* which encodes I_{k1} (Kir2.1) protein (Tawil-Anderson syndrome) (Tsuboi and Antzelevitch, 2006). Other potassium gene associated with LQT syndrome is *KCNJ5*, which encodes for Kir3.4 channel (also called GIRK4) (Yang et al., 2010). It forms homomeric channels or functional heteromeric channels with other Kir3.x, channels responsible for G protein-coupled inwardly rectifying potassium

channel current (IKACh) and mainly expressed in sinoatrial node, sinoventricular node and atria. A protein potassium-associated with LQT is A-kinase-anchoring proteins (AKAPs) 9, which is a scaffolding protein that determines the localization of protein kinase A (PKA) and other proteins that regulate the PKA (phosphatases or other kinases) (Chen et al., 2007). It is encoded by the *AKAP9* gene. Other sodium gene is *SCN4B* that encodes the beta subunit (NaVb4) of the sodium channel. The NaVb4 subunit causes a negative change in the sodium dependent voltage in the activation channel (Medeiros-Domingo et al., 2007). Recently, a pathogenic variant has been identified in the *SCN1B* gene as responsible of LQT syndrome. It encodes for two Navβ1 subunit cardiac isoforms: Navβ1 isoform a, and Navβ1 isoform b (Riuro et al., 2014). Focus on sodium associated proteins, *CAV3* encodes for caveolin-3, which is the main protein that forms the caveolae in cardiac and skeletal muscle (Vatta et al., 2006). The other sodium-associated protein is α1-Syntrophin, encoded by the *SNTA1* gene, a member of dystrophin-associated proteins that contains multiple protein interacting motifs (Wu et al., 2008). It has been also reported some genetic variants in calcium genes. Pathogenic variants in *CACNA1C* cause LQT syndrome Type 8 (Timothy syndrome) (Schwartz et al., 2006). This type of long QT syndrome is uncommon, but it has the highest associated mortality. Recently, few cases of LQT syndrome have been identified in two genes: *CALM1* and *CALM2*. These two genes together with *CALM3* encode for calmodulin protein, and their products have identical amino acid sequences, and all three are expressed in human heart left ventricle (Boczek et al., 2016; Reed et al., 2015). Calmodulin is a multifunctional Ca^{+2} binding protein essential for transduction of Ca^{+2} signals to influence the activity of cardiac ion channels, kinases, and other target proteins in heart. Finally, LQT syndrome has been also associated to *ANK2*, an associated calcium protein (Mohler et al., 2003). This gene encodes for Ankyrin-B protein. Ankyrins are adaptor proteins that link membrane proteins, transporters, and cell adhesion molecules to cytoskeleton. Variations in *ANK2* induces $\text{Na}^{+}/\text{Ca}^{+2}$ exchanger and $\text{Na}^{+}/\text{K}^{+}$ ATPase dysfunction producing cellular early and delayed after-depolarizations (EADs and DADs, respectively) in response to catecholamine.

Short QT Syndrome

Short QT syndrome (SQTS) is a very rare lethal entity described in 2000 (Gussak et al., 2000). It is characterized by a short QT interval ($\text{QTc} < 330$ ms), with a high sharp T wave and a short interval between the peak and the end of the T wave in the ECG. The severity of the clinical manifestations of SQTs is highly variable, ranging from asymptomatic to recurrent syncope and SCD. The age at onset of clinical manifestations may be extremely young with reports of malignant forms being responsible for even neonatal SCD (Mazzanti et al., 2014). Nowadays there is no pharmacological therapy of

proven efficacy to prevent arrhythmias and the implant of an ICD is the only alternative for high-risk cases. Quinidine has been tested as a treatment to try to prolong the QT. Few data is reported concerning exercise practice in SQTS. As adrenergic stress has not been linked with the development of life-threatening arrhythmias, nor competitive sports neither moderate leisure-time activity are allowed until more data is available (Ackerman et al., 2015).

Focusing on genetics, a limited number of pathogenic genetic variants have been associated with SQTS. These genetic alterations have been identified in 6 different genes (*KCNQ1*, *KCNJ2*, *KCNH2*, *CACNA1C*, *CACNB2*, and *CACNA2D1*), following an autosomal dominant pattern of inheritance (Behere and Weindling, 2015). It should be a high penetrance and a comprehensive genetic analysis identifies the genetic alteration in nearly 60% of clinically diagnosed cases. Type 1 short QT syndrome has been associated with genetic variants in *KCNH2* that induce a fast activation of potassium currents, with enhanced *I_{Kr}* function and shortened ventricular action potentials (Brugada et al., 2004). Type 2 short QT syndrome has been linked to genetic variant in *KCNQ1*, enhancing the function of the potassium channel, leading to a shortening of the action potential (Hong et al., 2005). Type 3 short QT syndrome is caused by genetic variants in *KCNJ2*, leading to an acceleration of the phase 3 action potential (Priori et al., 2005). Variants in calcium genes have been also reported. Two of these genes (*CACNA1C*, *CACNB2*) are associated with BrS and shortened QT interval, as abovementioned (Antzelevitch et al., 2007). The third calcium gene is *CACNA2D1* and only 1 pathogenic variant has been associated with SQTS (CM111612) (Templin et al., 2011).

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare cardiac entity characterized by a bidirectional polymorphic ventricular tachycardia characterized by severe arrhythmias in apparently normal hearts (Refaat et al., 2016). This syndrome is associated with a normal ECG at rest (occasionally with bradycardia, and U waves), and it is triggered by adrenergic stimulus and mainly expressed during exertion, extreme stress or emotion. It occurs mainly in children and adolescents and is increasingly recognized as a cause of unexplained SCD in young individuals, predominately in young males (30% by the age of 40 years) (Mohamed et al., 2007). It was thought that the event happened in childhood (before age 10) but recent studies show that the first manifestation may occur from infancy to age 40. Diagnosing CPVT can be difficult especially in young children. An exercise ECG and 24-h Holter monitoring can be very useful in order to rule out the bidirectional tachycardia in young, physically active children since CPVT cannot be diagnosed by a resting ECG or other cardiologic studies. The first line of therapy in patients with CPVT is beta-blockers, which have significantly reduced syncope and SCD.

Therapeutic guidelines are based on limited data; however, ICDs are indicated for patients with aborted SCD or CPVT during exercise and in adolescents with incompletely controlled CPVT despite a high dose of medications (Imberti et al., 2016). Cardiac sympathectomy has been also suggested to control CPVT in patients refractory to beta-blockers, although relief after this surgical procedure can be temporary or of delayed onset. The sport is contraindicated, including patients treated with beta-blockers (Ackerman et al., 2015).

Currently, CPVT is caused by impaired intracellular calcium handling due to nearly 200 pathogenic genetic variations in 5 different genes (*RyR2*, *CASQ2*, *KCNJ2*, *CALM1* and *TRDN*). All these genes together explain around 60% of CPVT cases. The main gene associated with CPVT is *RyR2*, being responsible of nearly 50% of all cases (Laitinen et al., 2001). The ryanodine receptor is an intracellular calcium channel that is located in the sarcoplasmic reticulum and activated by the influx of small amounts of calcium, thereby allowing the outflow of stored calcium, being crucial in triggering heart muscle contraction. Other gene associated with CPVT is *CASQ2* which encodes the cardiac muscle family member of the calsequestrin family that acts as an internal calcium store in muscle cells (Lahat et al., 2001). Two calcium associated proteins have been also reported in CPVT cases, Calmodulin (*CALM1*) (Marsman et al., 2014) and Triadin (*TRDN*) (Roux-Buisson et al., 2012). To date, only two genetic variants have been linked to CPVT (CM128791 and CM128792) in *CALM1*. Recently, a potential association of the *CALM2* gene in overlapping clinical features of LQTS and CPVT has been published despite remains to clarify its pathogenic role (Makita et al., 2014). Finally, Triadin (*TRDN*) is an integral membrane protein that contains a single transmembrane domain, involved in anchoring Calsequestrin to the junctional sarcoplasmic reticulum and allowing its functional coupling with the Ryanodine receptor that regulates sarcoplasmic reticulum calcium release. Focus on *KCNJ2*, few genetic variants have been associated with CPVT and it has been reported a variation (CM111211) in a patient showing Andersen-Tawil syndrome and CPVT mimicry.

CONCLUSION

In the last few years, cardiology has benefitted by improvement in genetics mainly applied to diagnosis and prevention of SCD. However, SCD remains an important cause of death mainly in young population. Despite several genes have been reported in ion channel diseases, large part of clinically diagnosed families remain without a genetic cause of disease recognized. In addition, early identification of individuals at risk and risk stratification are the main challenges of arrhythmogenic diseases associated with SCD. Thus, further studies in conjunction with families, clinicians, and basic researchers are required to clarify these points and adopt personalized preventive therapies.

REFERENCES

- Ackerman, M.J., Zipes, D.P., Kovacs, R.J., Maron, B.J., 2015. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 10: The Cardiac Channelopathies: A Scientific Statement From the American Heart Association and American College of Cardiology. *Circulation* 132, e326-329.
- Amin, A.S., Pinto, Y.M., Wilde, A.A., 2013. Long QT syndrome: beyond the causal mutation. *J. Physiol.* 591, 4125-4139.
- Antzelevitch, C., Pollevick, G.D., Cordeiro, J.M., Casis, O., Sanguinetti, M.C., Aizawa, Y., Guerchicoff, A., Pfeiffer, R., Oliva, A., Wollnik, B., Gelber, P., Bonaros, E.P., Jr., Burashnikov, E., Wu, Y., Sargent, J.D., Schickel, S., Oberheiden, R., Bhatia, A., Hsu, L.F., Haissaguerre, M., Schimpf, R., Borggrefe, M., Wolpert, C., 2007. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation* 115, 442-449.
- Arbelo, E., Brugada, J., 2014. Risk stratification and treatment of brugada syndrome. *Curr. Cardiol. Rep.* 16, 508.
- Basso, C., Carturan, E., Pilichou, K., Rizzo, S., Corrado, D., Thiene, G., 2010. Sudden cardiac death with normal heart Molecular autopsy. *Cardiovasc. Pathol.*
- Behere, S.P., Shubkin, C.D., Weindling, S.N., 2014. Recent advances in the understanding and management of long QT syndrome. *Curr. Opin. Pediatr.* 26, 727-733.
- Behere, S.P., Weindling, S.N., 2015. Inherited arrhythmias: The cardiac channelopathies. *Annals of pediatric cardiology* 8, 210-220.
- Bezzina, C.R., Barc, J., Mizusawa, Y., Remme, C.A., Gourraud, J.B., Simonet, F., Verkerk, A.O., Schwartz, P.J., Crotti, L., Dagradi, F., Guicheney, P., Fressart, V., Leenhardt, A., Antzelevitch, C., Bartkowiak, S., Borggrefe, M., Schimpf, R., Schulze-Bahr, E., Zumhagen, S., Behr, E.R., Bastiaenen, R., Tfelt-Hansen, J., Olesen, M.S., Kaab, S., Beckmann, B.M., Weeke, P., Watanabe, H., Endo, N., Minamino, T., Horie, M., Ohno, S., Hasegawa, K., Makita, N., Nogami, A., Shimizu, W., Aiba, T., Froguel, P., Balkau, B., Lantieri, O., Torchio, M., Wiese, C., Weber, D., Wolswinkel, R., Coronel, R., Boukens, B.J., Bezieau, S., Charpentier, E., Chatel, S., Despres, A., Gros, F., Kyndt, F., Lecoite, S., Lindenbaum, P., Portero, V., Violleau, J., Gessler, M., Tan, H.L., Roden, D.M., Christoffels, V.M., Le Marec, H., Wilde, A.A., Probst, V., Schott, J.J., Dina, C., Redon, R., 2013. Common variants at SCN5A-SCN10A and HEY2 are associated with Brugada syndrome, a rare disease with high risk of sudden cardiac death. *Nat. Genet.* 45, 1044-1049.
- Bianchi, L., Shen, Z., Dennis, A.T., Priori, S.G., Napolitano, C., Ronchetti, E., Bryskin, R., Schwartz, P.J., Brown, A.M., 1999. Cellular dysfunction of LQT5-minK mutants:

- abnormalities of IKs, IKr and trafficking in long QT syndrome. *Hum. Mol. Genet.* 8, 1499-1507.
- Boczek, N.J., Gomez-Hurtado, N., Ye, D., Calvert, M.L., Tester, D.J., Kryshnal, D.O., Hwang, H.S., Johnson, C.N., Chazin, W.J., Loporcaro, C.G., Shah, M., Papez, A.L., Lau, Y.R., Kanter, R., Knollmann, B.C., Ackerman, M.J., 2016. Spectrum and Prevalence of CALM1-, CALM2-, and CALM3-Encoded Calmodulin Variants in Long QT Syndrome and Functional Characterization of a Novel Long QT Syndrome-Associated Calmodulin Missense Variant, E141G. *Circ. Cardiovasc. Genet.* 9, 136-146.
- Brugada, P., Brugada, J., 1992. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J. Am. Coll. Cardiol.* 20, 1391-1396.
- Brugada, R., Campuzano, O., Sarquella-Brugada, G., Brugada, J., Brugada, P., 2014. Brugada syndrome. *Methodist DeBakey cardiovascular journal* 10, 25-28.
- Brugada, R., Hong, K., Dumaine, R., Cordeiro, J., Gaita, F., Borggrefe, M., Menendez, T.M., Brugada, J., Pollevick, G.D., Wolpert, C., Burashnikov, E., Matsuo, K., Wu, Y.S., Guerchicoff, A., Bianchi, F., Giustetto, C., Schimpf, R., Brugada, P., Antzelevitch, C., 2004. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 109, 30-35.
- Burashnikov, E., Pfeiffer, R., Barajas-Martinez, H., Delpon, E., Hu, D., Desai, M., Borggrefe, M., Haissaguerre, M., Kanter, R., Pollevick, G.D., Guerchicoff, A., Laino, R., Marieb, M., Nademanee, K., Nam, G.B., Robles, R., Schimpf, R., Stapleton, D.D., Viskin, S., Winters, S., Wolpert, C., Zimmern, S., Veltmann, C., Antzelevitch, C., 2010. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm* 7, 1872-1882.
- Campuzano, O., Allegue, C., Brugada, R., 2014a. [Genetics of sudden unexplained death]. *Medicina clinica* 142, 265-269.
- Campuzano, O., Allegue, C., Partemi, S., Iglesias, A., Oliva, A., Brugada, R., 2014b. Negative autopsy and sudden cardiac death. *International journal of legal medicine* 128, 599-606.
- Campuzano, O., Beltran-Alvarez, P., Iglesias, A., Scornik, F., Perez, G., Brugada, R., 2010. Genetics and cardiac channelopathies. *Genet. Med.* 12, 260-267.
- Cerrone, M., Delmar, M., 2014. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada syndrome. *Trends Cardiovasc. Med.* 24, 184-190.
- Cerrone, M., Lin, X., Zhang, M., Agullo-Pascual, E., Pfenniger, A., Chkourko Gusky, H., Novelli, V., Kim, C., Tirasawadichai, T., Judge, D.P., Rothenberg, E., Chen, H.S., Napolitano, C., Priori, S.G., Delmar, M., 2014. Missense mutations in plakophilin-2 cause sodium current deficit and associate with a Brugada syndrome phenotype. *Circulation* 129, 1092-1103.

- Chen, L., Marquardt, M.L., Tester, D.J., Sampson, K.J., Ackerman, M.J., Kass, R.S., 2007. Mutation of an A-kinase-anchoring protein causes long-QT syndrome. *Proc. Natl. Acad. Sci. US* 104, 20990-20995.
- Chen, Q., Kirsch, G.E., Zhang, D., Brugada, R., Brugada, J., Brugada, P., Potenza, D., Moya, A., Borggreffe, M., Breithardt, G., Ortiz-Lopez, R., Wang, Z., Antzelevitch, C., O'Brien, R.E., Schulze-Bahr, E., Keating, M.T., Towbin, J.A., Wang, Q., 1998. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature* 392, 293-296.
- Delpont, E., Cordeiro, J.M., Nunez, L., Thomsen, P.E., Guerchicoff, A., Pollevick, G.D., Wu, Y., Kanters, J.K., Larsen, C.T., Hofman-Bang, J., Burashnikov, E., Christiansen, M., Antzelevitch, C., 2008. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. *Circ. Arrhythm. Electrophysiol.* 1, 209-218.
- Giudicessi, J.R., Ackerman, M.J., 2013. Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. *Translational research: the journal of laboratory and clinical medicine* 161, 1-14.
- Giudicessi, J.R., Ye, D., Tester, D.J., Crotti, L., Mugione, A., Nesterenko, V.V., Albertson, R.M., Antzelevitch, C., Schwartz, P.J., Ackerman, M.J., 2011. Transient outward current (I_{to}) gain-of-function mutations in the KCND3-encoded Kv4.3 potassium channel and Brugada syndrome. *Heart Rhythm* 8, 1024-1032.
- Gussak, I., Brugada, P., Brugada, J., Wright, R.S., Kopecky, S.L., Chaitman, B.R., Bjerregaard, P., 2000. Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 94, 99-102.
- Hong, K., Piper, D.R., Diaz-Valdecantos, A., Brugada, J., Oliva, A., Burashnikov, E., Santos-de-Soto, J., Grueso-Montero, J., Diaz-Enfante, E., Brugada, P., Sachse, F., Sanguinetti, M.C., Brugada, R., 2005. De novo KCNQ1 mutation responsible for atrial fibrillation and short QT syndrome in utero. *Cardiovasc. Res.* 68, 433-440.
- Hu, D., Barajas-Martinez, H., Burashnikov, E., Springer, M., Wu, Y., Varro, A., Pfeiffer, R., Koopmann, T.T., Cordeiro, J.M., Guerchicoff, A., Pollevick, G.D., Antzelevitch, C., 2009. A mutation in the beta 3 subunit of the cardiac sodium channel associated with Brugada ECG phenotype. *Circ. Cardiovasc. Genet.* 2, 270-278.
- Hu, D., Barajas-Martinez, H., Terzic, A., Park, S., Pfeiffer, R., Burashnikov, E., Wu, Y., Borggreffe, M., Veltmann, C., Schimpf, R., Cai, J.J., Nam, G.B., Deshmukh, P., Scheinman, M., Preminger, M., Steinberg, J., Lopez-Izquierdo, A., Ponce-Balbuena, D., Wolpert, C., Haissaguerre, M., Sanchez-Chapula, J.A., Antzelevitch, C., 2014. ABCC9 is a novel Brugada and early repolarization syndrome susceptibility gene. *Int. J. Cardiol.* 171, 431-442.
- Imberti, J.F., Underwood, K., Mazzanti, A., Priori, S.G., 2016. Clinical Challenges in Catecholaminergic Polymorphic Ventricular Tachycardia. *Heart Lung Circ.*
- Ishikawa, T., Sato, A., Marcou, C.A., Tester, D.J., Ackerman, M.J., Crotti, L., Schwartz, P.J., On, Y.K., Park, J.E., Nakamura, K., Hiraoka, M., Nakazawa, K., Sakurada, H.,

- Arimura, T., Makita, N., Kimura, A., 2012. A novel disease gene for Brugada syndrome: sarcolemmal membrane-associated protein gene mutations impair intracellular trafficking of hNav1.5. *Circ. Arrhythm. Electrophysiol.* 5, 1098-1107.
- Kattygnarath, D., Maugenre, S., Neyroud, N., Balse, E., Ichai, C., Denjoy, I., Dilanian, G., Martins, R.P., Fressart, V., Berthet, M., Schott, J.J., Leenhardt, A., Probst, V., Le Marec, H., Hainque, B., Coulombe, A., Hatem, S.N., Guicheney, P., 2011. MOG1: a new susceptibility gene for Brugada syndrome. *Circ. Cardiovasc. Genet.* 4, 261-268.
- Lahat, H., Eldar, M., Levy-Nissenbaum, E., Bahan, T., Friedman, E., Khoury, A., Lorber, A., Kastner, D.L., Goldman, B., Pras, E., 2001. Autosomal recessive catecholamine- or exercise-induced polymorphic ventricular tachycardia: clinical features and assignment of the disease gene to chromosome 1p13-21. *Circulation* 103, 2822-2827.
- Laitinen, P.J., Brown, K.M., Piippo, K., Swan, H., Devaney, J.M., Brahmabhatt, B., Donarum, E.A., Marino, M., Tiso, N., Viitasalo, M., Toivonen, L., Stephan, D.A., Kontula, K., 2001. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation* 103, 485-490.
- London, B., Michalec, M., Mehdi, H., Zhu, X., Kerchner, L., Sanyal, S., Viswanathan, P.C., Pfahnl, A.E., Shang, L.L., Madhusudanan, M., Baty, C.J., Lagana, S., Aleong, R., Gutmann, R., Ackerman, M.J., McNamara, D.M., Weiss, R., Dudley, S.C., Jr., 2007. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na⁺ current and causes inherited arrhythmias. *Circulation* 116, 2260-2268.
- Makita, N., Yagihara, N., Crotti, L., Johnson, C.N., Beckmann, B.M., Roh, M.S., Shigemizu, D., Lichtner, P., Ishikawa, T., Aiba, T., Homfray, T., Behr, E.R., Klug, D., Denjoy, I., Mastantuono, E., Theisen, D., Tsunoda, T., Satake, W., Toda, T., Nakagawa, H., Tsuji, Y., Tsuchiya, T., Yamamoto, H., Miyamoto, Y., Endo, N., Kimura, A., Ozaki, K., Motomura, H., Suda, K., Tanaka, T., Schwartz, P.J., Meitinger, T., Kaab, S., Guicheney, P., Shimizu, W., Bhuiyan, Z.A., Watanabe, H., Chazin, W.J., George, A.L., Jr., 2014. Novel calmodulin mutations associated with congenital arrhythmia susceptibility. *Circ. Cardiovasc. Genet.* 7, 466-474.
- Marsman, R.F., Barc, J., Beekman, L., Alders, M., Dooijes, D., van den Wijngaard, A., Ratbi, I., Sefiani, A., Bhuiyan, Z.A., Wilde, A.A., Bezzina, C.R., 2014. A mutation in CALM1 encoding calmodulin in familial idiopathic ventricular fibrillation in childhood and adolescence. *J. Am. Coll. Cardiol.* 63, 259-266.
- Martin, C.A., Huang, C.L., Matthews, G.D., 2013. The role of ion channelopathies in sudden cardiac death: implications for clinical practice. *Ann. Med.* 45, 364-374.
- Mazzanti, A., Kanthan, A., Monteforte, N., Memmi, M., Bloise, R., Novelli, V., Miceli, C., O'Rourke, S., Borio, G., Zienciuk-Krajka, A., Curcio, A., Surducun, A.E., Colombo, M., Napolitano, C., Priori, S.G., 2014. Novel insight into the natural history of short QT syndrome. *J. Am. Coll. Cardiol.* 63, 1300-1308.

- Medeiros-Domingo, A., Kaku, T., Tester, D.J., Iturralde-Torres, P., Itty, A., Ye, B., Valdivia, C., Ueda, K., Canizales-Quinteros, S., Tusie-Luna, M.T., Makielski, J.C., Ackerman, M.J., 2007. SCN4B-encoded sodium channel beta4 subunit in congenital long-QT syndrome. *Circulation* 116, 134-142.
- Medeiros-Domingo, A., Tan, B.H., Crotti, L., Tester, D.J., Eckhardt, L., Cuoretti, A., Kroboth, S.L., Song, C., Zhou, Q., Kopp, D., Schwartz, P.J., Makielski, J.C., Ackerman, M.J., 2010. Gain-of-function mutation S422L in the KCNJ8-encoded cardiac K(ATP) channel Kir6.1 as a pathogenic substrate for J-wave syndromes. *Heart Rhythm* 7, 1466-1471.
- Mizusawa, Y., Horie, M., Wilde, A.A., 2014. Genetic and clinical advances in congenital long QT syndrome. *Circ. J.* 78, 2827-2833.
- Mohamed, U., Napolitano, C., Priori, S.G., 2007. Molecular and electrophysiological bases of catecholaminergic polymorphic ventricular tachycardia. *J. Cardiovasc. Electrophysiol.* 18, 791-797.
- Mohler, P.J., Schott, J.J., Gramolini, A.O., Dilly, K.W., Guatimosim, S., duBell, W.H., Song, L.S., Haurogne, K., Kyndt, F., Ali, M.E., Rogers, T.B., Lederer, W.J., Escande, D., Le Marec, H., Bennett, V., 2003. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 421, 634-639.
- Nakano, Y., Shimizu, W., 2016. Genetics of long-QT syndrome. *J. Hum. Genet.* 61, 51-55.
- Ohno, S., Zankov, D.P., Ding, W.G., Itoh, H., Makiyama, T., Doi, T., Shizuta, S., Hattori, T., Miyamoto, A., Naiki, N., Hancox, J.C., Matsuura, H., Horie, M., 2011. KCNE5 (KCNE1L) variants are novel modulators of Brugada syndrome and idiopathic ventricular fibrillation. *Circ. Arrhythm. Electrophysiol.* 4, 352-361.
- Oliva, A., Brugada, R., D'Aloja, E., Boschi, I., Partemi, S., Brugada, J., Pascali, V.L., 2010. State of the Art in Forensic Investigation of Sudden Cardiac Death. *Am. J. Forensic. Med. Pathol.*
- Priori, S.G., Blomstrom-Lundqvist, C., 2015. 2015 European Society of Cardiology Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death summarized by co-chairs. *Eur. Heart J.* 36, 2757-2759.
- Priori, S.G., Blomstrom-Lundqvist, C., Mazzanti, A., Blom, N., Borggrefe, M., Camm, J., Elliott, P.M., Fitzsimons, D., Hatala, R., Hindricks, G., Kirchhof, P., Kjeldsen, K., Kuck, K.H., Hernandez-Madrid, A., Nikolaou, N., Norekval, T.M., Spaulding, C., Van Veldhuisen, D.J., 2015. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 17, 1601-1687.

- Priori, S.G., Pandit, S.V., Rivolta, I., Berenfeld, O., Ronchetti, E., Dhamoon, A., Napolitano, C., Anumonwo, J., di Barletta, M.R., Gudapakkam, S., Bosi, G., Stramba-Badiale, M., Jalife, J., 2005. A novel form of short QT syndrome (SQT3) is caused by a mutation in the KCNJ2 gene. *Circ. Res.* 96, 800-807.
- Reed, G.J., Boczek, N.J., Etheridge, S.P., Ackerman, M.J., 2015. CALM3 mutation associated with long QT syndrome. *Heart Rhythm* 12, 419-422.
- Refaat, M.M., Hassanieh, S., Scheinman, M., 2016. Catecholaminergic Polymorphic Ventricular Tachycardia. *Cardiac electrophysiology clinics* 8, 233-237.
- Riuro, H., Beltran-Alvarez, P., Tarradas, A., Selga, E., Campuzano, O., Verges, M., Pagans, S., Iglesias, A., Brugada, J., Brugada, P., Vazquez, F.M., Perez, G.J., Scornik, F.S., Brugada, R., 2013. A missense mutation in the sodium channel beta2 subunit reveals SCN2B as a new candidate gene for Brugada syndrome. *Hum. Mutat.* 34, 961-966.
- Riuro, H., Campuzano, O., Arbelo, E., Iglesias, A., Batlle, M., Perez-Villa, F., Brugada, J., Perez, G.J., Scornik, F.S., Brugada, R., 2014. A missense mutation in the sodium channel beta1b subunit reveals SCN1B as a susceptibility gene underlying long QT syndrome. *Heart Rhythm* 11, 1202-1209.
- Roux-Buisson, N., Cacheux, M., Fourest-Lieuvain, A., Fauconnier, J., Brocard, J., Denjoy, I., Durand, P., Guicheney, P., Kyndt, F., Leenhardt, A., Le Marec, H., Lucet, V., Mabo, P., Probst, V., Monnier, N., Ray, P.F., Santoni, E., Tremeaux, P., Lacampagne, A., Faure, J., Lunardi, J., Marty, I., 2012. Absence of triadin, a protein of the calcium release complex, is responsible for cardiac arrhythmia with sudden death in human. *Hum. Mol. Genet.* 21, 2759-2767.
- Sanguinetti, M.C., Curran, M.E., Spector, P.S., Keating, M.T., 1996. Spectrum of HERG K⁺-channel dysfunction in an inherited cardiac arrhythmia. *Proc. Natl. Acad. Sci. US* 93, 2208-2212.
- Sarquella-Brugada, G., Campuzano, O., Arbelo, E., Brugada, J., Brugada, R., 2016. Brugada syndrome: clinical and genetic findings. *Genet. Med.* 18, 3-12.
- Schwartz, P.J., Spazzolini, C., Crotti, L., Bathen, J., Amlie, J.P., Timothy, K., Shkolnikova, M., Berul, C.I., Bitner-Glindzicz, M., Toivonen, L., Horie, M., Schulze-Bahr, E., Denjoy, I., 2006. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. *Circulation* 113, 783-790.
- Stallmeyer, B., Zumhagen, S., Denjoy, I., Duthoit, G., Hebert, J.L., Ferrer, X., Maugenre, S., Schmitz, W., Kirchhefer, U., Schulze-Bahr, E., Guicheney, P., 2012. Mutational spectrum in the Ca(2+)-activated cation channel gene TRPM4 in patients with cardiac conductance disturbances. *Hum. Mutat.* 33, 109-117.
- Templin, C., Ghadri, J.R., Rougier, J.S., Baumer, A., Kaplan, V., Albasa, M., Sticht, H., Rauch, A., Puleo, C., Hu, D., Barajas-Martinez, H., Antzelevitch, C., Luscher, T.F., Abriel, H., Duru, F., 2011. Identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome (SQTS6). *Eur. Heart J.* 32, 1077-1088.

- Tsuboi, M., Antzelevitch, C., 2006. Cellular basis for electrocardiographic and arrhythmic manifestations of Andersen-Tawil syndrome (LQT7). *Heart Rhythm* 3, 328-335.
- Ueda, K., Hirano, Y., Higashiuesato, Y., Aizawa, Y., Hayashi, T., Inagaki, N., Tana, T., Ohya, Y., Takishita, S., Muratani, H., Hiraoka, M., Kimura, A., 2009. Role of HCN4 channel in preventing ventricular arrhythmia. *J. Hum. Genet.* 54, 115-121.
- Vatta, M., Ackerman, M.J., Ye, B., Makielski, J.C., Ughanze, E.E., Taylor, E.W., Tester, D.J., Balijepalli, R.C., Foell, J.D., Li, Z., Kamp, T.J., Towbin, J.A., 2006. Mutant caveolin-3 induces persistent late sodium current and is associated with long-QT syndrome. *Circulation* 114, 2104-2112.
- Watanabe, H., Koopmann, T.T., Le Scouarnec, S., Yang, T., Ingram, C.R., Schott, J.J., Demolombe, S., Probst, V., Anselme, F., Escande, D., Wiesfeld, A.C., Pfeufer, A., Kaab, S., Wichmann, H.E., Hasdemir, C., Aizawa, Y., Wilde, A.A., Roden, D.M., Bezzina, C.R., 2008. Sodium channel beta1 subunit mutations associated with Brugada syndrome and cardiac conduction disease in humans. *J. Clin. Invest.* 118, 2260-2268.
- Wellens, H.J., Schwartz, P.J., Lindemans, F.W., Buxton, A.E., Goldberger, J.J., Hohnloser, S.H., Huikuri, H.V., Kaab, S., La Rovere, M.T., Malik, M., Myerburg, R.J., Simoons, M.L., Swedberg, K., Tijssen, J., Voors, A.A., Wilde, A.A., 2014. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur. Heart J.* 35, 1642-1651.
- Wu, G., Ai, T., Kim, J.J., Mohapatra, B., Xi, Y., Li, Z., Abbasi, S., Purevjav, E., Samani, K., Ackerman, M.J., Qi, M., Moss, A.J., Shimizu, W., Towbin, J.A., Cheng, J., Vatta, M., 2008. alpha-1-Syntrophin Mutation and the Long-QT Syndrome: A Disease of Sodium Channel Disruption. *Circ. Arrhythm. Electrophysiol.* 1, 193-201.
- Yang, Y., Liang, B., Liu, J., Li, J., Grunnet, M., Olesen, S.P., Rasmussen, H.B., Ellinor, P.T., Gao, L., Lin, X., Li, L., Wang, L., Xiao, J., Liu, Y., Zhang, S., Liang, D., Peng, L., Jespersen, T., Chen, Y.H., 2010. Identification of a Kir3.4 mutation in congenital long QT syndrome. *Am. J. Hum. Genet.* 86, 872-880.

Chapter 2

EARLY REPOLARIZATION

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ABSTRACT

For more than 70 years, early repolarization has been considered a common normal variant. In the general population, the prevalence ranges between 5 and 13%, and in athletes, a rising trend is observed from 20 to 90%. Nevertheless, from the latter half of the 1990s, a growing number of case reports, series, observational and retrospective studies reported that the presence of various electrocardiographic patterns attributed to early repolarization may constitute a potential marker for the increased risk of sudden death in otherwise normal individuals, casting a dark shadow on this ECG peculiarity. J wave syndromes include a group of disorders sharing similar pathophysiologic mechanisms, characterized by ≥ 1 mm J point elevation with or without ST segment elevation. They basically include Brugada syndrome, early repolarization syndrome, ST segment elevation myocardial infarction, and hypothermia. Although a substantial proportion of individuals with elevated J point remain asymptomatic, others may present isolated early coupled ventricular premature beats, runs of non sustained ventricular tachycardia, sustained ventricular tachycardia, or ventricular fibrillation and sudden cardiac death.

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INTRODUCTION

About 10% of the sudden cardiac death (SCD) cases are related to primary electrophysiological disorders with known (e.g., Brugada Syndrome) or unknown ion-channel pathologies (Brugada, 1998; Zipes, 1998; Moss, 1985; Gaita, 2003; Corrado, 2001, Viskin, 1990; Huikuri, 2001).

Early repolarization Syndrome (ERS), with Brugada Syndrome (BrS), is a part of the so called J-Wave Syndromes (JWSs). ERS and BrS are thought to represent two different manifestations of the JWSs. Both syndromes are associated with the development of polymorphic VT and VF, leading to SCD in young adults with no apparent structural heart disease and, occasionally, to sudden infant death syndrome. An ER pattern (ERP) is often encountered in apparently healthy individuals, particularly in young males, black individuals, and athletes (Biasco, 2013). ERP is also observed in acquired conditions, including hypothermia and ischemia (Bastiaenen, 2010; Federman, 2013). When associated with VT/VF in the absence of structural heart disease, ERP is referred to ERS.

The prevalence of an ERP in the inferior and/or lateral leads with a J-point elevation ≥ 0.1 mV ranges between 1% and 24%, with a J-point elevation ≥ 0.2 mV ranges between 0.6% to 6.4% (Tikkanen, 2009; Sinner 2010; Haruta 2011). No significant regional differences in the prevalence of an ERP have been reported (Hayashi 2015). However, ERP is significantly more common in blacks than in caucasians. Moreover, some regional differences in the manifestation of ERS has been reported, for example ERP appears to be more common in Aboriginal Australians than in Caucasian Australians (Brosnan, 2015).

The clinical and prognostic impacts of ER were first clearly exposed in 2008 (Haïssaguerre, 2008) and, thereafter, a large number of new studies and researches was performed. Recently was held a specifically consensus conference focused on ERS (Antzelevitch, 2016), according to the last guidelines for inherited primary arrhythmia syndromes (Priori, 2013) and to previous consensus conferences dedicated to BrS (Wilde, 2002; Antzelevitch, 2005). In relation to ER, the lack of agreement regarding the terminology has led to a great confusion and inconsistency reporting in literature.

This chapter is focused on ER as a cause of SCD. We provide a general review, based on past and recent studies and an overview over clinical perspective.

HISTORICAL BACKGROUND

The electrocardiographic pattern defined as early repolarization (ER) has been considered for a long time a common normal variant, since its first description by Shipley and Hallaran in 1936 (Shipley, 1936). These authors analyzed the ECGs of medical

students and young nurses finding the common presence of a terminal QRS slurring or notching, defined, respectively, as ‘a momentary retardation of string movement’ or ‘an actual change in direction of the string movement’ (Figure 1A). In the same years some patterns, subsequently associated to ERP due to their electrocardiographic appearance, were described. Following reports were relatively imprecise and inconsistent in describing the same ECG finding. In 1938, Tomaszewski presented the case of an accidentally frozen man whose ECG demonstrated a very slowly inscribed deflection between the QRS complex and the earliest part of the ST segment, representing a J wave (Tomaszewski, 1938). In 1953, Osborn described a “current of injury” later named “the Osborn wave” in acidotic and hypothermic dogs at rectal temperatures $<25^{\circ}\text{C}$ (Osborn, 1953). In 1961, Wasserburger et al. defined ER as a 1-4 mm takeoff of the ST-segment at the end of the QRS complex, with a distinct notch or slur on the downslope of the R wave, in the mid to left precordial leads (Wasserburger, 1961) (Figure 1B). In 1977, Friedman et al. defined the early repolarization as abnormal variant characterized by the presence of a notch at the transition of the QRS complex into the ST segment, the latter with a concave upward displacement of 2 or even 3 mm in the precordial leads and, occasionally, in the peripheral leads and tall, broad-based and upright T waves (Friedman, 1977) (Figure 1C). In 1988, Schamroth used the term “early repolarization syndrome, vagotonia, the athlete’s heart” to indicate uncommon normal pattern characterized by the presence of a thickening or slurring of the terminal part of the QRS that may appear as a distinct notch or ‘hook’ on the distal limb of the QRS complex, associated with concave upward elevated ST segment, tall and symmetrical T waves and other minor characteristics (Schamroth, 1988) (Figure 1D).

The interest in early repolarization was mainly oriented in differentiating this common and possibly misleading pattern, from other conditions such as acute myocardial infarction, pericarditis, hyperkalemia or hypothermia also characterized by a displacement of the ST segment. Finally, a remarkable work confirmed the benign nature of the early repolarization pattern together with the characteristic features of a prevalent manifestation in male, black, young and physically active individuals (Goldman, 1953; Grusin, 1954).

The benign nature of an ERP was challenged in 2000s (Gussak, 1999), based on experimental data showing that this ECG manifestation predisposes to the development of polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) in coronary-perfused wedge preparations (Gussak, 2000; Yan, 1999; Shu, 2005). In the same year, an evidence supporting this hypothesis was provided by Kalla et al. and Takagi et al.

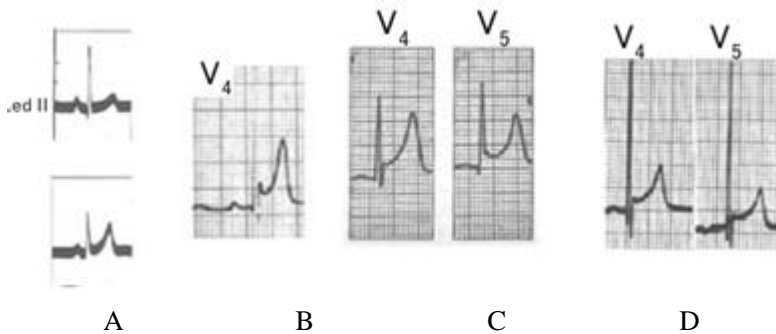


Figure 1. Different ERPs presented by Shipley and Hallaran (A), Wasserburger (B), Friedman (C) and Schamroth (D).

Kalla et al. described in 2000 the similar case of a 29-year-old Vietnamese patient resuscitated after a nocturnal episode of ventricular fibrillation. The electrocardiogram recorded a prominent J wave (labeled by the author Osborn wave, like the terminal QRS slurring commonly observed during hypothermia) with ST-segment elevation mainly evident in leads II, III, and aVF. Of note, the authors described dynamic changes of the ECG pattern observed at serial monitoring during hospitalization. The authors interpreted this electrocardiographic pattern as a Brugada syndrome variant (Kalla, 2000). In the same year Takagi et al. reported two cases of nocturnal idiopathic ventricular fibrillation and one case of nocturnal syncope with inducible ventricular fibrillation in otherwise healthy young men. The ECGs were characterized by a terminal slurring of the QRS complex (labeled J wave) in the inferior leads. A 24-h ECG recording revealed infrequent or no PVCs in all three patients. Intravenous disopyramide increased ST-segment elevation in the inferior leads, whereas treadmill testing caused the ST-segment elevation to decrease or disappear at peak exercise. Also in this article, the similarities with the clinical and the dynamic electrocardiographic presentation of Brugada syndrome were highlighted (Takagi, 2000).

In 2008, Haïssaguerre et al., Nam et al. and Rosso et al. finally identified ER as a new arrhythmic disorder, describing a strong relationship between J-waves and many different forms of ventricular arrhythmias in the absence of known heart disease (Haïssaguerre, 2008; Nam, 2008; Rosso, 2008).

Haïssaguerre et al. published a case-control retrospective study that compared the electrocardio-graphic characteristics of 206 patients with idiopathic ventricular fibrillation with those of 412 controlled healthy individuals. In this work a new definition of early repolarization was proposed representing a turning point from previous classical descriptions. Haïssaguerre et al. also adopted the definition of early repolarization as a J-point elevation more than 1 mm in inferior and/or lateral leads irrespective of the morphology of the ST segment, that was not taken into consideration. The prevalence of this redefined early repolarization was significantly higher in ventricular fibrillation cases versus controls (31 versus 5%, $P < 0.001$). Moreover, cases showed a significantly higher

J-point elevation that became even more evident in concomitance of an arrhythmic event. Haissaguerre's patients also were more frequently men, they had frequent arrhythmic events in the early hours of the morning and were protected by oral quinidine.

In the same year, Rosso et al. added complexity defining the transition of the QRS-ST segment as 'J-point elevation or J wave,' when a positive notch was evident during the terminal portion of the QRS complex (Figure 2 A) or 'slurred' when the R wave gradually merged into the ST segment, with upright concavity without a clearly evident J point (Figure 2 B). The presence of a J-point elevation was confirmed to be more common in patients with idiopathic ventricular fibrillation than in young control individuals or athletes. The 'J-point elevation or J wave,' but not the morphology of the ST segment or the location of the J waves (anterolateral versus inferior leads), was thus recognized as a possible marker of increased arrhythmic risk.

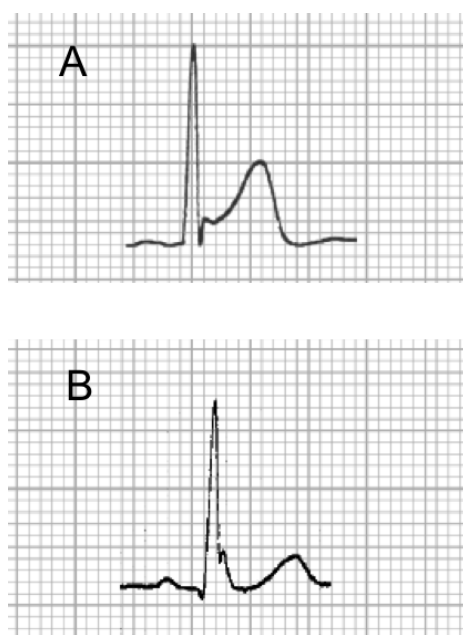


Figure 2. Morphologies of the QRS-ST transition presented and defined as: (A) J-point elevation and (B) slurring.

Some recent large-scale retrospective and prospective studies have identified a particular sub-group of individuals with clinical (young, man) and ECG characteristics (a markedly anomalous transition of the QRS complex into the ST segment defined by a significant, dynamic J-point elevation in the inferior leads, occasionally associated with inverted T waves), that may be at increased risk for sudden death if compared with the general population. This risk has also estimated to be 3.4 of 100 000 in the normal population, 11 of 100 000 in participants with J-point elevation and 34 of 100 000 in the presence of J-point elevation and horizontal ST segment (Rosso, 2011).

CELLULAR BACKGROUND

The JWSs (BrS and ERS) are characterized by the presence of a prominent J wave.

Some studies have shown that the J wave is related to a transmural voltage gradient caused by the manifestation of an action potential (AP) notch in epicardium but not endocardium, due to a heterogeneous transmural distribution of I_{to} (Yan, 1996). An end of QRS notch, similar to a J wave, was proposed to be due to intraventricular conduction delays. The 2 ECG manifestations can be distinguished based on their response to rate, with the latter showing accentuation at faster rates (Macfarlane, 2015). Differences between J wave and intraventricular conduction delay (IVCD)-mediated syndromes are summarized in Table 1.

Table 1. Differential diagnosis of JWSs vs IVCD (from Antzelevitch et al. [17])

	JWSs	IVCD
Male predominance	yes	No
Average age at clinical presentation	Young adults	Old adults
Common morphology	Dome-like appearance	Sharp appearance
Response to heart rate	Bradycardia-dependent augmentation of J wave (+/- T-wave inversion)	Tachycardia-dependent augmentation of the notch
Concomitant structural heart disease	Rare	Common (CAD)

When analyzing the cellular background of ERS, it is mandatory to consider the ERS as a part of JWS, so studying it together with BrS.

Two principal electrophysiological mechanism have been formulated to explain the ECG and clinical manifestations of BrS: (1) *The repolarization hypothesis*, that asserts an outward shift in the balance of currents in RV epicardium, that can lead to repolarization abnormalities leading to development of phase 2 reentry, which generates closely coupled premature beats able to trigger VT/VF; (2) *The depolarization hypothesis*, that suggests the presence of slow conduction area in the RVOT, secondary to fibrosis and reduced connexin 43 (Cx43), leading to discontinuities in conduction, plays a primary role in the development of the ECG and arrhythmic manifestations of the syndrome (Wilde, 2010). The typical response of BrS to acceleration of rate is diminution of ST-segment elevation, opposite to that expected at a site of discontinuous conduction. The diminution of ST-segment elevation is consistent with the reduced availability of I_{to} at the faster rate, due to slow recovery of the current from inactivation.

These two theories are not mutually exclusive and could act together in the development of the clinical manifestations.

The strongest evidence in support of the depolarization hypothesis derives from the observational studies showing that radiofrequency ablation (RFA) of epicardial sites display late potentials and fractionated bipolar electrograms in the RVOT of patients with BrS, significantly reduced the arrhythmia vulnerability as well as the ECG manifestation of the syndrome (Nademanee, 2011). Similar results were reported by Brugada et al. (Brugada, 2015) and by Sacher et al. (Sacher, 2014) who also observed in an isolated case that accentuation of the Brugada ECG by ajmaline was associated with an increased area of low-voltage and fragmented electrogram activity. A wider area of low-voltage activity was associated with a more prominent ST-segment elevation. These authors concluded that the late potentials and fractionated electrogram activity are due to conduction delays within the RVOT/RV anterior wall and the ablation of the sites of slow conduction is the basis for the ameliorative effect of ablation therapy.

Similarly to the mechanisms of BrS, an accentuation of transmural gradients in the LV wall are responsible for the repolarization abnormalities present in ERS, leading to J-point elevation, J wave or slurred QRS (Koncz, 2014). This repolarization defect is accentuated by cholinergic agonists and reduced by quinidine, isoproterenol, cilostazol, and milrinone, accounting for the ability of these agents to reverse the repolarization abnormalities responsible for ERS (Aizawa, 2015). Higher intrinsic levels of I_{to} in the inferior LV were also shown to underlie the greater vulnerability of the inferior LV wall to VT/VF.

Conduction delay is known to give rise to notching of the QRS complex; when it occurs on the rising phase of the R wave, it is due to a conduction defect within the ventricle, when it occurs at the terminal portion of the QRS, thus masquerading as a J wave, it may be due to either a conduction defect or a repolarization defect (Antzelevitch, 2013). The response to prematurity or to an increase in rate can differentiate between the two (Antzelevitch, 2015). Delayed conduction becomes greater at faster heart rates or during premature beats, thus leading to accentuation of the QRS notch, whereas repolarization defects usually are mitigated, resulting in diminution of the J wave at faster rates.

The prognostic value of a fragmented QRS has been demonstrated in BrS (Priori, 2012) but fragmentation of the QRS is not associated with increased risk in the absence of cardiac disease. The congruence between BrS and ERS with respect to clinical manifestations and response to therapy lends further support to the repolarization hypothesis.

GENETIC BACKGROUND

The key gene in the pathophysiology of BrS is SCN5A, a gene coding for a subunit of a sodium channel. However, more than 300 BrS-related variants in SCN5A have been

described (Kapplinger, 2010). Loss-of-function mutations in *SCN5A* contribute to the development of both BrS and ERS, as well as to a lot of other conduction diseases. The current evidence suggests that the presence of a prominent I_{to} determines whether loss-of-function mutations resulting in a reduction in I_{Na} will manifest a BrS/ERS or other conduction disease (Szel, 2014).

Figure 3 shows the overlap syndromes attributable to genetic defects in *SCN5A*.

Focusing on ERS, it is known that an ERP has been shown to be familial (Reinhard, 2011). ERP and ERS have been associated with variants in 7 genes (Table 2). Consistent with the findings that I_{K-ATP} activation can generate an ERP in canine ventricular wedge preparations, variants in *KCNJ8* and *ABCC9*, responsible for the poreforming and ATP-sensing subunits of the I_{K-ATP} channel, have been reported in patients with ERS (Barajas-Martinez, 2012). Loss-of-function variations in the $\alpha 1$, $\beta 2$, and $\alpha 2\delta$ subunits of the cardiac L-type calcium channel (*CACNA1C*, *CACNB2*, *CACNA2D1*) and the $\alpha 1$ subunit of $Na_v1.5$ and $Na_v1.8$ (*SCN5A*, *SCN10A*) have been reported in patients with ERS (Watanabe, 2011; Hu, 2014).

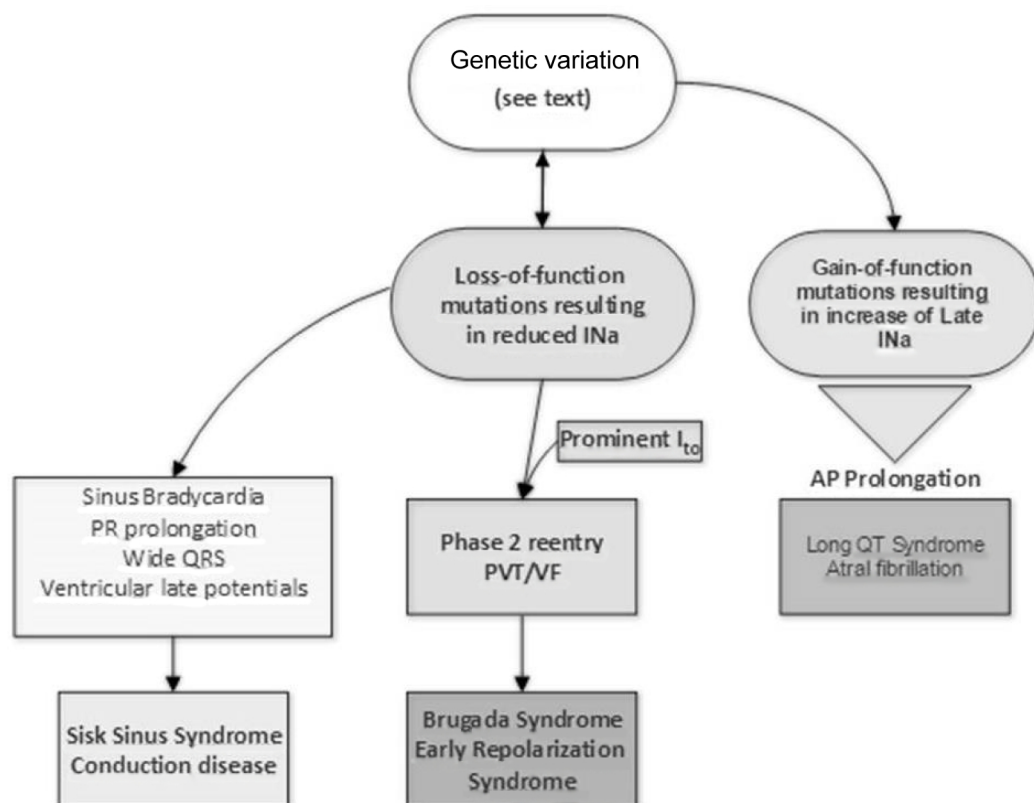


Figure 3. Possible clinical manifestation caused by a loss-of-function or a gain-of-function mutation in the involved genes (see text for explanation).

Table 2. Genetic mutations associated with ERS

Gene Defects Associated with ERS				
	Locus	Gene/Protein	Ion channel	% of proband
ERS1	12p11.23	KCNJ8, Kir6.1	↑ I _{K-ATP}	Rare
ERS2	12p13.3	CACNA1C, Cav1.2	↓ I _{Ca}	4.1%
ERS3	10p12.33	CACNB2b, Cavβ2b	↓ I _{Ca}	8.3%
ERS4	7q21.11	CACNA2D1, Cava2δ1	↓ I _{Ca}	4.1%
ERS5	12p12.1	ABCC9, SUR2A	↑ I _{K-ATP}	Rare
ERS6	3p21	SCN5A, Nav1.5	↓ I _{Na}	Rare
ERS7	3p22.2	SCN10A, Nav1.8	↓ I _{Na}	Rare

It is mandatory to specify that only a small fraction of identified genetic variants in the genes associated with JWSs have been studied using functional expression tests to assess causality and establish a probable contribution to pathogenesis. Only few genes have been studied in genetically engineered animal models, and less more have been studied in cardiac cells or in induced pluripotent stem cell-derived cardiac myocytes isolated from ERS and BrS patients. Computational strategies, used to predict the functional consequences of mutations, are helpful but these methods have not been rigidly tested. The absence of biologic or functional validation of mutation effects is a great limitation of genetic test interpretation, as recently pointed out by Schwartz et al. (Schwartz, 2013). To date, there are more than 20 JWSs involved genes (Antzelevitch, 2012). All these genes have magnified the issues of interpretation adding confusion without significantly increase the genetic-based diagnosis. One study revealed that the 4% of individuals in the NHLI GO Exome Sequencing Project (GO-ESP) population possess a previously published BrS-associated variant that would prompt a “positive” genetic test (Risgaard, 2013).

These issues reinforce the necessity to interpret JWS genetic test results as “probabilistic” rather than diagnostic. This could be explained because JWSs may not be due to a single mutation but rather to inheritance of multiple genetic susceptibility variants acting in concert through one or more different pathways.

Probst et al. shown that in 5 of 13 large families with a SCN5A mutation, the genotype did not co-segregate with the phenotype (Probst, 2009). In addition to the multifactorial nature of the genetics, expressivity of the syndromes may be multifactorial and the genetic predisposition can be modulated by hormonal and other environmental factors, or morphologic changes (fibrosis) (Nademanee, 2015).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

ERS is generally diagnosed in patients who have ER in the inferior and/or lateral leads presenting with aborted cardiac arrest, documented VF, or polymorphic VT.

An early repolarization pattern (ERP) of ECG, consist of a distinct J-wave or J-point elevation, or a notch or slur of the terminal part of the QRS with and without an ST-segment elevation.

A recent expert consensus report, focused on the terminology of ER, recommends that the peak of an end QRS notch and/or the onset of an end QRS slur be designated as J_p ; that J_p should exceed 0.1 mV in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG for ER to be present. It was further recommended that the start of the end QRS notch or J wave be designated as J_o and the termination as J_t (Macfarlane, 2015). An end-QRS notch is a notch that occurs on the final 50% of the downslope of an R-wave occurring as the final segment of the QRS complex; it links with the ST-segment (Figure 4A). It should be distinguished from a notch midway on the downslope of an R-wave (Figure 4B), because this may be due to fragmentation. Similarly, an end-QRS slur is an apparent slowing of the inscription of the waveform at the end of the QRS complex that merges with the ST-segment of the complex. Similarly, a slur should occur in the final 50% of the R-wave downslope.

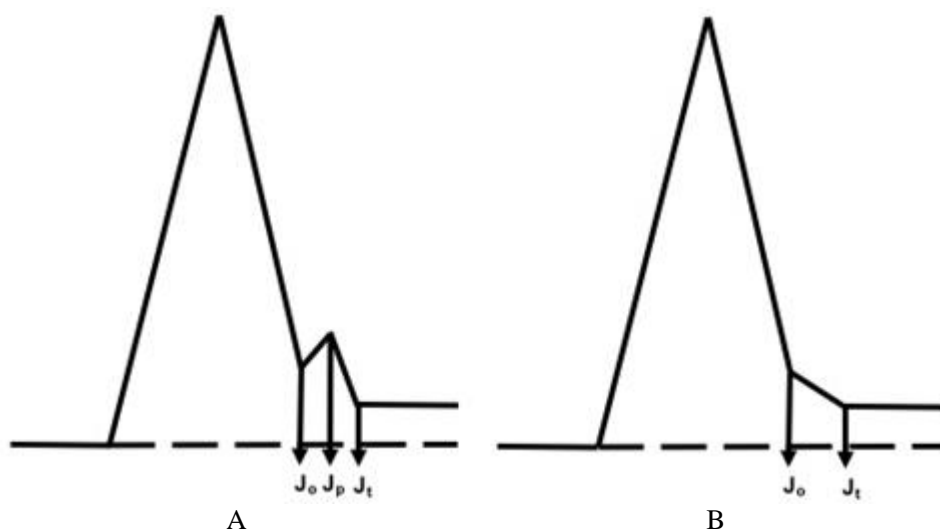


Figure 4. (A) Illustration of the amplitudes J onset (J_o), J peak (J_p), and J termination in an end-QRS notched (J_t). (B) Illustration of J_p and J_t in an end-QRS slur.

Avoiding confusion about correct definition, a recent consensus paper, introduced a “standard” definition of ER. Early repolarization is present if all of the following criteria are met:

1. There is an end-QRS notch or slur on the down-slope of a prominent R-wave. If there is a notch, it should lie entirely above the baseline. The onset of a slur must also be above the baseline.
2. J_p is ≥ 0.1 mV in 2 or more contiguous leads of the 12-lead ECG, excluding leads V1 to V3.
3. QRS duration is <120 ms.

If the ST-segment is upward sloping and followed by an upright T-wave, the pattern should be described as “early repolarization with an ascending ST segment.”

If the ST-segment is horizontal or downward sloping, the pattern should be described as “early repolarization with a horizontal or descending ST segment.” The leads in which the notching or slurring occurs should be used as part of the description, so that, for example, a complete report might state, “Early repolarization with horizontal ST-segment in inferior leads (II, III and aVF).”

The consensus view is that ST-segment elevation in the absence of a slur or notch should not be reported as early repolarization.

QRS complex duration should be obtained manually from the standard 12-lead ECG and should ideally be done from the leads without the early repolarization pattern so that the overall QRS duration will not be overestimated (automated measurement of QRS duration generally uses measurements from all leads, including those with notches, so overestimate the real QRS duration).

Localization of ER (J_o elevation, notch or slur of the terminal part of the QRS and ST-segment or J_t elevation) over the 12-lead ECG allow to recognize three different types of ER (Antzelevic, 2010):

1. Type 1: when ECG changes are present in the lateral leads;
2. Type 2: when they are present in infero-lateral leads and;
3. Type 3: when they are in the infero-lateral + anterior *or* right ventricular leads.

Table 3 lists some clinical patterns with overlapping ECG appearance, in the differential diagnosis of ERS, while Table 4 lists the Expert Consensus diagnostic criteria for ERS.

A proposed diagnostic score system for ERS, referred as the Proposed Shanghai ERS Score, is presented in Table 5. The scoring system is based on evidence available in the present literature. Points are based on expert opinion informed by cohort studies that do not include all variables presented. Thus, precise, objectively weighted coefficients were not derived from large-scale risk factor- and outcome-informed data study.

Table 3. Clinical patterns with overlapping ECG appearance with ER

ER differential diagnosis
STEMI (anteroseptal myocardial infarction)
Myocardial ischemia
Hypertensive heart disease
Takotsubo cardiomyopathy
Myocarditis
Cocaine use
Juvenile ST pattern
Aortic dissection
ARVC (Arrhythmogenic right ventricular cardiomyopathy)
Athlete's heart
Pericardial disease (pericarditis, pericardial cyst, pericardial tumor)
Hypothermia
Hyperthermia
Hypocalcemia
Hyperpotassemia
Myocardial tumor (lipoma)
Fragmented QRS (terminal notching)
Thymoma
Neurologic causes (intracerebral bleeding, acute brain injury)
Chagas disease

**Table 4. Early Repolarization Syndrome criteria
(Expert Consensus recommendation)**

Expert Consensus Recommendations on Early Repolarization Syndrome (ERS) Diagnosis
ER syndrome is diagnosed in the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT
ER syndrome can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
ER pattern can be diagnosed in the presence of J-point elevation ≥ 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

Table 5. Proposed Shanghai Score for ERS

Proposed Shanghai Score System for diagnosis of early repolarization syndrome	
	Points
Clinical History	
Unexplained cardiac arrest, documented VF or polymorphic VT	3
Suspected arrhythmic syncope	2
Syncope of unclear mechanism/unclear etiology	1
12-lead ECG	
ER ≥ 0.2 mV in ≥ 2 inferior and/or lateral ECG leads with horizontal/descending ST segment	2
Dynamic changes in J-point elevation (≥ 0.1 mV) in ≥ 2 inferior and/or lateral ECG leads	1.5
≥ 0.1 mV J-point elevation in at least 2 inferior and/or lateral ECG leads	1
ECG monitoring	
Short-coupled PVCs with R on ascending limb or peak of T wave	2
Family History	
Relative with definite ERS	2
≥ 2 first-degree relatives with a “IIa” ECG pattern	2
First-degree relative with “IIa” ECG pattern	1
Unexplained sudden cardiac death <45 years in a first-or second-degree relative	0.5
Genetic Test Result	
Probable pathogenic ERS susceptibility mutation	0.5
Score (with at least 1 ECG finding):	
≥ 5 points: Probable/Definite ERS	
3-4.5 points: possible ERS	
<3 points: Non diagnostic	

As evident from available literature it is clear that ERS have several similarities with BrS. Male predominance is present in both syndromes with prevalence between 71 and 96% (Benito, 2008; Kamakura, 2013); Japanese have higher prevalence than in other cohort studies.

In both syndromes, the highest incidence of SCD come in the third decade of life, potentially related to testosterone levels in males (Matsumoto, 2003).

In both syndromes, the J wave and the ST-segment elevation become more prominent during bradycardia or pauses; this explain because SCD often occurs during night or during rest (Aizawa, 2012).

ERS and BrS also share similarities with respect to the response to pharmacologic therapy. In both, electrical storms and associated J-wave manifestations can be suppressed using β -adrenergic agonists (Watanabe, 2006). Chronic oral pharmacologic therapy using quinidine, bepridil, denopamine, and cilostazol is reported to suppress the

development of VT/VF in both ERS and BrS secondary to inhibition of I_{to} , augmentation of I_{Ca} , or both (Haissaguerre, 2009).

On the other hand, differences between the two syndromes include:

1. the region of the heart most affected (RVOT vs inferior LV) (Nagase, 2002);
2. the presence of (minimal) structural abnormalities in BrS but not in ERS;
3. the incidence of late potentials in signal-averaged ECGs (SAECGs) (BrS 60% vs ERS 7%);
4. greater elevation of J_o , J_p , or J_t (ST-segment elevation) in response to sodium channel blockers in BrS vs ERS and higher prevalence of atrial fibrillation in BrS vs ERS (McIntyre, 2012).

Early studies suggested a different pathophysiologic basis for ERS and BrS based on the observation that sodium channel blockers unmask or accentuate J-wave manifestation in BrS but reduces the amplitude in ERS; however, the recent study by Nakagawa et al. showed that J waves recorded using unipolar LV epicardial leads, introduced into the left lateral coronary vein in ERS patients, are indeed augmented, even though J waves recorded in the lateral precordial leads are diminished, due principally to engulfment of the surface J wave by the widened QRS (Nakagawa, 2014).

The principal difference between BrS and ERS is related to the region of the ventricle most affected. Epicardial mapping studies in BrS patients report accentuated J waves and fragmented and/or late potentials in the epicardial region of the RVOT, whereas in ERS only accentuated J waves, particularly in the inferior wall of LV, are observed (Ghosh, 2010). Fractionated electrogram activity and late potentials have been observed in experimental models of ERS but have not yet been reported clinically. Non invasive mapping electroanatomic studies have reported very steep localized repolarization gradients across the inferior/lateral regions of LV of ERS patients, preceded by normal ventricular activation, whereas in BrS both slow discontinuous conduction and steep dispersion of repolarization are present in the RVOT (Zhang, 2015). Another presumed difference is the presence of structural abnormalities in BrS, which have not yet been described in ERS. Although J waves are accentuated or induced by both hypothermia and fever, the development of arrhythmias in ERS is much more sensitive to hypothermia, and arrhythmogenesis in BrS appears to be promoted only by fever (Bastiaenen, 2010; Federman, 2013). Hypothermia has been reported to increase the risk of VF in ERS, and fever is well recognized as a major risk factor in BrS. It is noteworthy that hypothermia can diminish the manifestation of a BrS ECG when already present. An ERP is associated with an increased risk for VF in patients with acute myocardial infarction and hypothermia (Patel, 2010; Gurabi, 2014). A concomitant ERP in the inferolateral leads has also been reported to be associated with an increased risk of arrhythmic events in

patients with BrS. Kawata et al. reported that the prevalence of ER in inferolateral leads was high (63%) in BrS patients with documented VF (Kawata, 2013).

RISK STRATIFICATION

The key problem in evaluating patients with ERP is to assess its relative risk to develop a VF/SCD. The casual finding of a J wave on routine screening ECG should not be interpreted as a marker of risk for SCD because the odds for this fatal disease are approximately 1:10,000 (Viskin, 2014). However, a careful attention it is necessary to identify patients with “high risk” ER. In general, there are two different appearance of J wave over the 12-lead ECG: (1) a notched wave, with a “classical” J-wave distinct from the QRS and (2), a “slurred” ER, with the J wave included in the terinal part of QRS, resulting in an elevation of J_o. Patients with a distinct J wave have a worse prognosis than patients with a “slurred” J wave.

Like the BrS, there are some “strong” risk factor like: (1) history of unexplained syncope likely due to VT/VF (or cardiac arrest) and (2) present of prominent J wave in all leads.

All the studies using the diagnostic criteria of Haissaguerre for diagnosis of ERS have shown that ERP predicts SCD.

Several studies show a clear association between ER and death from all causes, cardiovascular death and arrhythmic death.

The J wave or ER is recognized to predispose to the development of malignant arrhythmia when associated with other cardiac disorders, such as ischemia, heart failure, and hypothermia. The J wave might predict prognosis of cardiac events in various heart diseases, and the appearance of a new J wave during acute ischemia seems to be a signal of possible VF. For this reason, there is a great debate regarding whether ER represents a primary electrical disorder or a substrate facilitating ventricle arrhrhymias under certain circumstances.

Family history of sudden death in subjects with ERP has been identified as a risk factor (Nunn, 2011).

In BrS patient’s population, it is known that ERP is a marker of high risk as documented by Conte et al.; they shown that fragmented QRS and ERP are common ECG findings in high-risk BrS patients, occurring in up to 27% of cases. When combined, f-QRS and ERP confer a higher risk of appropriate ICD interventions during a very long-term follow-up (Conte, 2016).

ER in the Athletes

The classical early repolarization pattern appears to be the rule in the athletes, being manifest in a large percentage of the athletic population. From an historical perspective, the surge of interest toward early repolarization in athletes is evident from the second half of the 1960s (Nakamoto, 1969; Gibbons, 1977).

Of interest, for more than 40 years some characteristics associated with early repolarization, such as a male prevalence, the increased incidence in athletes of black ethnicity, the heart rate dependency of its appearance and the possible effect of an increased vagal tone as a mechanistic determinant of the pattern were almost unanimously adopted by researchers as a “dogma.”

The necessity of a clear discrimination between training-related ECG changes and pathological findings was even more perceived in that historical setting in whom the only noninvasive imaging technique available was limited to the chest radiograph.

Nonetheless nowadays, despite the significant development of imaging techniques, very little is changed from what Lichtman et al. described in 1973: ‘routine medical evaluations of well trained endurance athletes frequently disclose electrocardiographic abnormalities suggestive of organic heart disease. First- and second-degree atrioventricular block, altered ventricular conduction, criteria for atrial enlargement or ventricular hypertrophy, and repolarization abnormalities are commonly found. On the basis of such abnormal tracings, the athlete may be advised to refrain from his customary strenuous exertion, even though the results of physical examination are normal and there is no history suggesting cardiovascular disease (Lichtman, 1973).

Renewed interest in early repolarization arose in the 1990s after the description of the Brugada syndrome, interest justified by substantial analogies in terms of possible overlapping electrocardiographic appearances, shared electrophysiological mechanism (i.e., an increased transmural dispersion of repolarization) and the modulating effects of b-blockers

Bianco et al. in 2001 showed that a more accurate differential diagnosis between “traditional” early repolarization pattern and suspected Brugada morphology was necessary only in a small percentage of top-level athletes (about 8%, i.e., those with ST elevation limited to the right precordial leads with a ‘convex toward the top morphology’) (Bianco, 2001).

As stated before, after the work published on the New England Journal of Medicine by Haissaguerre et al. the introduction of a newly defined early repolarization had a groundbreaking effect causing the complete collapse of the common belief about its benign significance.

Noseworthy et al. were the first that reevaluated the problem of early repolarization in athletes facing this new scenario. Using Haissaguerre’s definition of early repolarization, they reported a prevalence of J-point elevation of 25.1% in 879 US

collegiate athletes. The pattern was primarily evident in the lateral leads (V4-V6, I and aVL) rather than in the inferior leads (21.3 versus 2.5%); J-point elevation was rarely at least 2 mm in two or more contiguous leads (2% of the population studied). An ascending elevation of the ST segment was evident almost universally (99% in lateral leads and 55% in inferior leads), whereas a horizontal or descending ST segment was rare (1.7%) (Noseworthy, 2011).

Another remarkable feature in athletes is that early repolarization is substantially stable; it only becomes less evident during exercise and disappears in case of prolonged detraining, while waxing and waning of the abnormalities of the QRS - ST transition are known to occur in patients with ventricular arrhythmias.

Biasco et al. published a retrospective analysis performed in a relatively large population of 332 elite professional football players. In this series the incidence of J-point elevation was 35.6%, no cardiovascular deaths were observed at a long-term follow-up (median of 13.3 years). At multivariable analysis, the known inverse association with heart rate was confirmed while a strong signal in the direction of a potential mechanistic role of left ventricular hypertrophy was also evident (Biasco, 2013).

Nonetheless, we focus that the last position paper regarding the evaluation for athletic participants to prevent SCD, consider the presence of ERP in athletes like a physiological adaptation and so they do not suggest any further evaluation (Mont, 2016).

THERAPY

Table 6 present recommendations for the management of ERS as illustrated in the 2013 HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes and the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD. Those recommendations are based on the available literature and on the clinical experience of the Task Force members. As with all such recommendations, they will need to undergo continuous validation in future studies.

A therapeutic approach in the field of JWSs is established for BRs patients, in which education and lifestyle changes are critical for the prevention of arrhythmias; patients should be informed of the various modulators and precipitating factors that could cause malignant arrhythmias. For ERS, at this moment, there are no evident based recommendations to avoid ventricular arrhythmias recurrences.

**Table 6. Early Repolarization Syndrome therapeutic intervention
(Expert Consensus recommendation)**

Expert Consensus Recommendations on Early Repolarization Therapeutic Interventions	
Class I	1. ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest.
Class IIa	2. Isoproterenol infusion can be useful in suppressing electrical storms in patients with a diagnosis of ER syndrome. 3. Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome
Class IIb	4. ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation >1 mm in 2 or more inferior or lateral leads 5. ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation.
Class III	1. ICD implantation is not recommended asymptomatic patients with an isolated ER ECG pattern.

Implantable Cardioverter Defibrillator Therapy

The only proven effective therapeutic strategy for the prevention of SCD in high-risk BrS and ERS patients is an ICD (Brugada, 2000).

It is important to recognize that ICDs are associated with complications, especially in young active individuals (Conte, 2015). At 10 years postimplantation, the rates of inappropriate shock and lead failure are 37% and 29%, respectively. Remote monitoring can identify lead failure and prevent inappropriate shocks (Sacher, 2009). Subcutaneous ICDs are thought to represent the future for this indication because they are expected to be associated with fewer complications over a lifetime (De Maria, 2015).

Implantation of an ICD is first-line therapy for JWS patients presenting with aborted SCD or documented VT/VF (Class I recommendation).

At present, there is no clear role for PES in patients with ERS.

Pacemaker Therapy

Arrhythmic events and SCD in both BrS and ERS generally occur during sleep or at rest and are associated with slow heart rates. These observations establish a potential therapeutic role for cardiac pacing but there are only few case reports, limited to BrS (Bertomeu-Gonzalez, 2006).

Radiofrequency Ablation Therapy

There are no clinical reports of ablation of the LV substrate in patients with ERS. In patients in whom BrS combines with ERS, ablation of the anterior RV epicardium (including the RVOT) is not ameliorative on the ERP.

Pharmacologic Therapy

Pharmacologic therapy of ERS is similar to BrS, confirming that the underlying mechanism are similar. Quinidine, phosphodiesterase III inhibitors and isoproterenol have all been shown to exert an ameliorative effect in preventing or quieting arrhythmias associated with ERS. Isoproterenol has been shown to be effective in quieting electrical storms developing in patients with ERS (Haissaguerre, 2009). Isoproterenol has been shown to act by reversing the repolarization abnormalities responsible for the disease phenotype secondary to restoration of the epicardial AP dome in experimental models of ERS (Koncz, 2014). This action of the beta-adrenergic agonist is expected because of its actions to potentially increase I_{Ca} .

The phosphodiesterase III inhibitor cilostazol has been reported to reduce the ECG and arrhythmic manifestations of ERS (Iguchi, 2013). Phosphodiesterase inhibitors are known to activate I_{Ca} secondary to an increase in cAMP. The augmentation of I_{Ca} is thought to prevent arrhythmias associated with JWS by reversing the repolarization defects and restoring electrical homogeneity across the ventricular wall secondary to restoration of the epicardial AP dome in ERS (Gurabi, 2014). Cilostazol has been hypothesized to also block I_{to} . Augmentation of I_{Ca} together with inhibition of I_{to} are expected to produce an inward shift in the balance of currents active during the early phases of the epicardial AP that should be especially effective in suppressing J-wave activity. The effectiveness of bepridil in ERS has been reported just once (Aizawa, 2013).

CONCLUSION AND FUTURE PERSPECTIVE

Because of the high prevalence of ERP and relatively low risks of arrhythmia in patients with this condition, counseling and management are particularly challenging. There is a strong need to understand when individuals with ERP are at significantly elevated risks of arrhythmic events, identifying some risk criteria helping the cardiologist to stratify clearly the risk of SCD. The heterogeneous frequency of arrhythmic events in individuals with ERP makes challenging the identification of efficacious interventions that may reduce arrhythmic risk. Although both quinidine and isoproterenol are effective

for the management of patients with VF and electrical storms, evidence-based data remain limited to small samples with limited follow-up. The proper indication to prescribe such medications remains unclear and, whether there is any role for medical therapy in a primary prevention setting, it is unknown. It remains unknown if, in patients with ERP, exist some avoidable triggers (e.g., medications) of arrhythmic events. The prognostic significance of exercise training, which is associated with an increased prevalence of ERP, similarly remains unclear even if some studies do not show an augmented arrhythmic risk.

The latest international Expert consensus statement on the diagnosis and management of patients with inherited arrhythmia syndromes do not focus attention on primary prevention because of the lack of current evidences.

As previously noted, the risk of SCD in asymptomatic patients without a family history of SCD is very low, and further investigation or treatment is not indicated on the basis of current data.

Patients with potentially arrhythmic syncope or a family history of sudden cardiac death should be evaluated further with respect to high-risk clinical features.

We think that a large-scale international registry could help to identify missing factors to stratify better the patients and establish a clear approach to risk stratification of patients with ERP.

REFERENCES

- Aizawa Y, Chinushi M, Hasegawa K, Naiki N, Horie M, Kaneko Y, Kurabayashi M, Ito S, Imaizumi T, Aizawa Y, Takatsuki S, Joo K, Sato M, Ebe K, Hosaka Y, Haissaguerre M, Fukuda K. 2013 "Electrical storm in idiopathic ventricular fibrillation is associated with early repolarization." *J. Am. Coll. Cardiol.* 62:1015-1019.
- Aizawa Y, Sato A, Watanabe H, Chinushi M, Furushima H, Horie M, Kaneko Y, Imaizumi T, Okubo K, Watanabe I, Shinozaki T, Aizawa Y, Fukuda K, Joo K, Haissaguerre M. 2012 "Dynamicity of the J-wave in idiopathic ventricular fibrillation with a special reference to pause-dependent augmentation of the J-wave." *J. Am. Coll. Cardiol.* 59:1948-1953.
- Aizawa Y, Sato M, Kitazawa H, Aizawa Y, Takatsuki S, Oda E, Okabe M, Fukuda K. 2015 "Tachycardia-dependent augmentation of "notched J waves" in a general patient population without ventricular fibrillation or cardiac arrest: Not a repolarization but a depolarization abnormality?" *Heart Rhythm* 12: 376-383.
- Antzelevitch C, Brugada P, Borggreffe M et al. 2005 "Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association." *Circulation* 111:659-670.
- Antzelevitch C, Yan GX. 2010 "J wave syndromes." *Heart Rhythm* 7:549-558.

- Antzelevitch C, Yan GX. 2015 "J-wave syndromes: Brugada and early repolarization syndromes." *Heart Rhythm* 12:1852-1866.
- Antzelevitch C. 2013 "J wave syndromes: molecular and cellular mechanisms." *J. Electrocardiol.* 46:510-518.
- Antzelevitch C. 2012 "Genetic, Molecular and cellular mechanisms underlying the J wave syndromes." *Circ. J.* 76:1054-1065.
- Barajas-Martinez H, Hu D, Ferrer T et al. 2012 "Molecular genetic and functional association of Brugada and early repolarization syndromes with S422L missense mutation in KCNJ8." *Heart Rhythm* 9:548-555.
- Bastiaenen R, Hedley PL, Christiansen M, Behr ER. 2010 "Therapeutic hypothermia and ventricular fibrillation storm in early repolarization syndrome." *Heart Rhythm*; 7:832-834.
- Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, Arzamendi D, Berne P, Brugada R, Brugada P, Brugada J. 2008 "Gender differences in clinical manifestations of Brugada syndrome." *J. Am. Coll. Cardiol.* 52: 1567-1573.
- Bertomeu-Gonzalez V, Ruiz-Granell R, Garcia-Civera R, Morell-Cabedo S, Ferrero A. 2006 "Syncope monomorphic ventricular tachycardia with pleomorphism, sensitive to antitachycardia pacing in a patient with Brugada syndrome." *Europace* 8:1048-1050.
- Bianco M, Bria S, Gianfelici A, Sanna N, Palmieri V, Zeppilli P. 2001 "Does early repolarization in the athlete have analogies with the Brugada syndrome?" *Eur. Heart J.* 22:504-510.
- Biasco L., Cristoforetti Y, Castagno D, Giustetto C, Astegiano P, Ganzit G, Gribaudo CG, Gaita F. 2013 "Clinical, Electrocardiographic, Echocardiographic Characteristics and Long Term Follow up of Elite Soccer Players with J Point Elevation." *Circ. Arrhythm. Electrophysiol.* 6:1178-84.
- Brosnan MJ, Kumar S, LaGerche A, Brown A, Stewart S, Kalman JM, Prior DL. 2015 "Early repolarization patterns associated with increased arrhythmic risk are common in young non-Caucasian Australian males and not influenced by athletic status." *Heart Rhythm* 12:1576-1583.
- Brugada J, Brugada R, Brugada P. 1998 "Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease." *Circulation*; 97: 457-460.
- Brugada J, Brugada R, Brugada P. 2000 "Pharmacological and device approach to therapy of inherited cardiac diseases associated with cardiac arrhythmias and sudden death." *J. Electrocardiol.* 33(Suppl):41-47.
- Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciccone G, Giannelli L, Santinelli V. 2015 "Brugada syndrome phenotype elimination by epicardial substrate ablation." *Circ. Arrhythm. Electrophysiol.* 8: 1373-1381.
- Charles Antzelevitch, Gan-Xin Yan, Michael J. Ackerman, Martin Borggrefe, Domenico Corrado, Jihong Guo, Ihor Gussak, Can Hasdemir, Minoru Horie, Heikki Huikuri, Changsheng Ma, Hiroshi Morita, Gi-Byoung Nam, Frederic Sacher, Wataru Shimizu, Sami Viskin, Arthur A.M. Wilde. 2016 "J-Wave syndromes expert consensus

- conference report: Emerging concepts and gaps in knowledge.” *Europace*. Oct;32(5):315-339.
- Conte G, Sieira J, Ciconte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, La Meir M, Wellens F, Czapla J, Wauters K, Levinstein M, Saitoh Y, Irfan G, Julià J, Pappaert G, Brugada P. 2015 “Implantable cardioverter-defibrillator therapy in Brugada syndrome: a 20-year single-center experience.” *J. Am. Coll. Cardiol.* 65:879-888.
- Conte G, de Asmundis C, Sieira J, Ciconte G, Di Giovanni G, Chierchia GB, Casado-Arroyo R, Baltogiannis G, Ströker E, Irfan G, Pappaert G, Auricchio A, Brugada P. 2016 “Prevalence and Clinical Impact of Early Repolarization Pattern and QRS-Fragmentation in High-Risk Patients With Brugada Syndrome.” *Circ. J.* Sep. 23;80(10):2109-16.
- Corrado D, Basso C, Thiene G. 2001 “Sudden cardiac death in young people with apparently normal heart.” *Cardiovasc. Res.* 50:399-408.
- De Maria E, Olaru A, Cappelli S. 2015 “The entirely subcutaneous defibrillator (S-ICD): state of the art and selection of the ideal candidate.” *Curr. Cardiol. Rev.* 11:180-186.
- Federman NJ, Mechulan A, Klein GJ, Krahn AD. 2013 “Ventricular fibrillation induced by spontaneous hypothermia in a patient with early repolarization syndrome.” *J. Cardiovasc. Electrophysiol.* 24:586-588.
- Friedman HH. 1977 “Diagnostic electrocardiography and vectorcardiography,” 2nd ed. McGraw-Hill; p. 71.
- Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. 2003 “Short QT Syndrome: a familial cause of sudden death.” *Circulation* 108:965-970.
- Ghosh S, Cooper DH, Vijayakumar R, Zhang J, Pollak S, Haissaguerre M, Rudy Y. 2010 “Early repolarization associated with sudden death: insights from noninvasive electrocardiographic imaging.” *Heart Rhythm* 7:534-537.
- Gibbons L, Cooper K, Martin R et al. 1977 “Medical examination and electrocardiographic analysis of elite distance runners.” *Ann. N Y Acad. Sci.* 301:283-296.
- Goldman MJ. 1953 “RS-T segment elevation in mid and left precordial leads as a normal variant.” *Am. Heart J.* 46:817-820.
- Grusin H. 1954 “Peculiarities of the Africans electrocardiogram and changes observed in serial studies.” *Circulation*; 9:860-887.
- Gurabi Z, Koncz I, Patocskaï B, Nesterenko VV, Antzelevitch C. 2014 “Cellular mechanism underlying hypothermia-induced VT/VF in the setting of early repolarization and the protective effect of quinidine, cilostazol and milrinone.” *Circ. Arrhythm. Electrophysiol.* 7:134-142.
- Gurabi Z, Koncz I, Patocskaï B, Nesterenko VV, Antzelevitch C. 2014 “Cellular mechanism underlying hypothermia-induced VT/VF in the setting of early repolarization and the protective effect of quinidine, cilostazol and milrinone.” *Circ. Arrhythm. Electrophysiol.* 7:134-142.

- Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR. 1999 "The Brugada syndrome: clinical, electrophysiologic and genetic aspects." *Journal of the American College of Cardiology* 33: 5-15.
- Gussak I, Antzelevitch C. 2000 "Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms." *J. Electrocardiol.* 33: 299-309.
- Haïssaguerre M, Chatel S, Sacher F, Weerasooriya R, Probst V, Loussouarn G, Horlitz M, Liersch R, Schulze-Bahr E, Wilde A, Käb S, Koster J, Rudy Y, Le Marec H, Schott JJ. 2009 "Ventricular fibrillation with prominent early repolarization associated with a rare variant of KCNJ8/KATP channel." *J. Cardiovasc. Electrophysiol.* 20:93-98.
- Haïssaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquié JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clémenty J. 2008 "Sudden cardiac arrest associated with early repolarization." *N. Engl. J. Med.* 358:2016-2023.
- Haïssaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquié JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P, Clémenty J. 2009 "Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy." *J. Am. Coll. Cardiol.* 53:612-619.
- Haruta D, Matsuo K, Tsuneto A, Ichimaru S, Hida A, Sera N, Imaizumi M, Nakashima E, Maemura K, Akahoshi M. 2011 "Incidence and prognostic value of early repolarization pattern in the 12-lead electrocardiogram." *Circulation* 123:2931-2937.
- Hayashi M, Shimizu W, Albert CM. 2015 "The spectrum of epidemiology underlying sudden cardiac death." *Circ. Res.* 116:1887-1906.
- Hu D, Barajas-Martinez H, Pfeiffer R et al. 2014 "Mutations in SCN10A are responsible for a large fraction of cases of Brugada syndrome." *Journal of the American College of Cardiology* 64:66-79.
- Huikuri HV, Castellanos A, Myerburg RJ. 2001 "Sudden death due to cardiac arrhythmias." *N. Engl. J. Med.* 345:1473-1482.
- Iguchi K, Noda T, Kamakura S, Shimizu W. 2013 "Beneficial effects of cilostazol in a patient with recurrent ventricular fibrillation associated with early repolarization syndrome." *Heart Rhythm* 10:604-606.
- Kalla H, Yan GX, Marinchak R. 2000 "Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant?" *J. Cardiovasc. Electrophysiol.* 11: 95-98.
- Kamakura T, Kawata H, Nakajima I, Yamada Y, Miyamoto K, Okamura H, Noda T, Satomi K, Aiba T, Takaki H, Aihara N, Kamakura S, Kimura T, Shimizu W. 2013 "Significance of non-type 1 anterior early repolarization in patients with inferolateral early repolarization syndrome." *J. Am. Coll. Cardiol.* 62:1610-1618.

- Kapplinger JD, Tester DJ, Alders M et al. 2010 "An international compendium of mutations in the SCN5A encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing." *Heart Rhythm* 7:33-46.
- Kawata H, Morita H, Yamada Y, Noda T, Satomi K, Aiba T, Isobe M, Nagase S, Nakamura K, Fukushima Kusano K, Ito H, Kamakura S, Shimizu W. 2013 "Prognostic significance of early repolarization in inferolateral leads in Brugada patients with documented ventricular fibrillation: a novel risk factor for Brugada syndrome with ventricular fibrillation." *Heart Rhythm* 10:1161-1168.
- Koncz I, Gurabi Z, Patocskaï B, Panama BK, Szel T, Hu D, Barajas-Martinez H, Antzelevitch C. 2014 "Mechanisms underlying the development of the electrocardiographic and arrhythmic manifestations of early repolarization syndrome." *J. Mol. Cell. Cardiol.* 68C:20-28.
- Koncz I, Gurabi Z, Patocskaï B, Panama BK, Szel T, Hu D, Barajas-Martinez H, Antzelevitch C. 2014 "Mechanisms underlying the development of the electrocardiographic and arrhythmic manifestations of early repolarization syndrome." *J. Mol. Cell. Cardiol.* 68C:20-28.
- Lichtman J, O'Rourke RA, Klein A, Karliner JS. 1973 "Electrocardiogram of the athlete. Alterations simulating those of organic heart disease." *Arch. Intern. Med.* 132:763-770.
- Macfarlane P, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen J, Wellens H, Yan GX. 2015 "The early repolarization pattern: consensus paper." *Journal of the American College of Cardiology* 66:470-477.
- Macfarlane P, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, Sacher F, Tikkanen J, Wellens H, Yan GX. 2015 "The early repolarization pattern: consensus paper." *J. Am. Coll. Cardiol* 66:470-477.
- Matsumoto AM. 2003 "Fundamental aspects of hypogonadism in the aging male." *Rev. Urol.* 5(Suppl. 1):S3-S10.
- McIntyre WF, Perez-Riera AR, Femenia F, Baranchuk A. 2012 "Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially over-lapping entities." *J. Electrocardiol.* 45:195-198.
- Mont L, Pelliccia A, Sharma S, Biffi A, Borjesson M, Terradellas JB, Carré F, Guasch E, Heidbuchel H, Gerche A, Lampert R, McKenna W, Papadakis M, Priori SG, Scanavacca M, Thompson P, Sticherling C, Viskin S, Wilson M, Corrado D. 2017 "Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE." *Europace*. Jan;19(1):139-163.
- Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. 1985 "The long QT syndrome: a prospective international study." *Circulation* 71: 17-21.
- Nademanee K, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, Makita N, Kowase S, Boonmee N, Vitayakritsirikul V, Ratanarapee S, Sharma S, van der Wal AC, Christiansen M, Tan HL, Wilde AA, Nogami A, Sheppard MN, Veerakul G, Behr ER. 2015 "Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome." *J. Am. Coll. Cardiol.* 66:1976-1986.

- Nademanee K, Veerakul G, Chandanamattha P, Chaothawee L, Ariyachaiporn A, Jirasirojanakorn K, Likittanasombat K, Bhuripanyo K, Ngarmukos T. 2011 "Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium." *Circulation* 123:1270-1279.
- Nagase S, Kusano KF, Morita H, Fujimoto Y, Kakishita M, Nakamura K, Emori T, Matsubara H, Ohe T. 2009 "Epicardial electrogram of the right ventricular outflow tract in patients with the Brugada syndrome: using the epicardial lead." *J. Am. Coll. Cardiol.* 39:1992-1995.
- Nakamoto K. 1969 "Electrocardiograms of 25 marathon runners before and after 100 meter dash." *Jpn. Circ. J.* 33:105-126.
- Nam GB, Kim YH, Antzelevitch C. 2008 "Augmentation of J waves and electrical storms in patients with early repolarization." *N. Engl. J. Med.* 358: 2078-2079.
- Noseworthy PA, Weiner R, Kim J, Keelara V, Wang F, Berkstresser B, Wood MJ, Wang TJ, Picard MH, Hutter AM Jr, Newton-Cheh C, Baggish AL. 2011 "Early repolarization pattern in competitive athletes: clinical correlates and the effects of exercise training." *Circ. Arrhythm. Electrophysiol.* 4:432-440.
- Nunn LM, Bhar-Amato J, Lowe MD, Macfarlane PW, Rogers P, McKenna WJ, Elliott PM, Lambiase PD. 2011 "Prevalence of J-point elevation in sudden arrhythmic death syndrome families." *J. Am. Coll. Cardiol.* 58:286-290.
- Osborn JJ. 1953 "Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function." *Am. J. Physiol.*, 175: 389-398.
- Patel RB, Ng J, Reddy V, Chokshi M, Parikh K, Subacius H, Sheikh-Ali AA, Nguyen T, Link MS, Goldberger JJ, Ilkhanoff L, Kadish AH. 2010 "Early repolarization associated with ventricular arrhythmias in patients with chronic coronary artery disease" *Circ. Arrhythm. Electrophysiol.* 3: 489-495.
- Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, Sassone B, Giordano U, Pappone C, Mascioli G, Rossetti G, De Nardis R, Colombo M. 2012 "Risk stratification in Brugada syndrome: results of the PRELUDE (Programmed electrical stimulation predictive value) registry." *Journal of the American College of Cardiology* 59:37-45.
- Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. 2013 "Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes." *Heart Rhythm.* Dec;10(12):e85-108.
- Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. 2013 "HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013." *Heart Rhythm* Dec;10(12):1932-63.

- Probst V, Wilde AA, Barc J, Sacher F, Babuty D, Mabo P, Mansourati J, Le Scouarnec S, Kyndt F, Le Caignec C, Guicheney P, Gouas L, Albuissou J, Meregalli PG, Le Marec H, Tan HL, Schott JJ. 2009 "SCN5A mutations and the role of genetic background in the pathophysiology of Brugada syndrome." *Circ. Cardiovasc. Genet.* 2:552-557.
- Reinhard W, Kaess BM, Debiec R, Nelson CP, Stark K, Tobin MD, Macfarlane PW, Tomaszewski M, Samani NJ, Hengstenberg C. 2014 "Heritability of early repolarization: a population-based study." *Circ. Cardiovasc. Genet.* 4: 134-138.
- Risgaard B, Jabbari R, Refsgaard L, Holst AG, Haunso S, Sadjadieh A, Winkel BG, Olesen M, Tfelt-Hansen J. 2013 "High prevalence of genetic variants previously associated with Brugada syndrome in new exome data." *Clin. Genet.* 84: 489-495.
- Rosso R, Adler A, Halkin A, Viskin S. 2011 "Risk of sudden death among young individuals with J waves and early repolarization: putting the evidence into perspective." *Heart Rhythm* 8:923-929.
- Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. 2008 "J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance." *J. Am. Coll. Cardiol.* 52:1231-1238.
- Sacher F, Jesel L, Jais P, Haissaguerre M. 2014 "Insight into the mechanism of Brugada syndrome: epicardial substrate and modification during ajmaline testing." *Heart Rhythm* 11:732-734.
- Sacher F, Probst V, Bessouet M, Wright M, Maluski A, Abbey S, Bordachar P, Deplagne A, Ploux S, Lande G, Jaïs P, Hocini M, Haïssaguerre M, Le Marec H, Clémenty J. 2009 "Remote implantable cardioverter defibrillator monitoring in a Brugada syndrome population." *Europace* 11: 489-494.
- Schamroth L. 1988 "*The 12 lead electrocardiogram*," 2nd ed. Blackwell Scientific; pp. 97-99.
- Schwartz PJ, Ackerman MJ, George AL Jr., Wilde AA. 2013 "Impact of genetics on the clinical management of channelopathies." *Journal of the American College of Cardiology* 62: 169-180.
- Shipley RA, Hallaran WR. 1936 "The four-lead electrocardiogram in two hundred normal men and women." *Am. Heart J.* 11:325-345.
- Shu J, Zhu T, Yang L, Cui C, Yan GX. 2005 "ST-segment elevation in the early repolarization syndrome, idiopathic ventricular fibrillation, and the Brugada syndrome: cellular and clinical linkage." *J. Electrocardiol.* 38:26-32.
- Sinner MF, Reinhard W, Müller M, Beckmann BM, Martens E, Perz S, Pfeufer A, Winogradow J, Stark K, Meisinger C, Wichmann HE, Peters A, Riegger GA, Steinbeck G, Hengstenberg C, Kääb S. 2010 "Association of early repolarization pattern on ECG with risk of cardiac and all-cause mortality: a population-based prospective cohort study (MONICA/KORA)." *PLoS Med.* Jul. 27;7(7):e1000314.
- Szel T, Antzelevitch C. 2014 "Abnormal repolarization as the basis for late potentials and fractionated electrograms recorded from epicardium in experimental models of Brugada syndrome." *Journal of the American College of Cardiology* 63:2037-2045.
- Takagi M, Aihara N, Takaki H, Taguchi A, Shimizu W, Kurita T, Suyama K, Kamakura S. 2000 "Clinical characteristics of patients with spontaneous or inducible ventricular

- fibrillation without apparent heart disease presenting with J wave and ST segment elevation in inferior leads.” *J. Cardiovasc. Electrophysiol.* 11: 844-848.
- Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. 2009 “Long-term outcome associated with early repolarization on electrocardiography.” *N. Engl. J. Med.* 361:2529-2537.
- Tomaszewski W. 1938 “Changement electrocardiographiques observes chez un home mort de froid.” *Arch. Mal. Coeur. Vaiss.* 31: 525-528.
- Viskin S, Adler A, Halkin A, Rosso R. 2014 “Reply: is the J wave or the ST slope malignant...or neither?” *J. Am. Coll. Cardiol.* 63:1812-1813.
- Viskin S, Belhassen B. 1990 “Idiopathic ventricular fibrillation.” *Am. Heart J.* 120:661-671.
- Wasserburger RH, Alt WJ. 1961 “The normal RS-T segment elevation variant.” *Am. J. Cardiol.* 8: 184-192.
- Watanabe A, Fukushima KK, Morita H, Miura D, Sumida W, Hiramatsu S, Banba K, Nishii N, Nagase S, Nakamura K, Sakuragi S, Ohe T. 2006 “Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome.” *Eur. Heart J.* 27:1579-1583.
- Watanabe H, Nogami A, Ohkubo K et al. 2011 “Electrocardiographic characteristics and SCN5A mutations in idiopathic ventricular fibrillation associated with early repolarization.” *Circ. Arrhythm. Electrophysiol.* 4:874-881.
- Wilde AA, Antzelevitch C, Borggreffe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. 2002 “Proposed diagnostic criteria for the Brugada syndrome: consensus report.” *Circulation* 106:2514-2519.
- Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, Antzelevitch C. 2010 “The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization.” *J. Mol. Cell. Cardiol.* 49: 543-553.
- Yan GX, Antzelevitch C. 1996 “Cellular basis for the electrocardiographic J wave.” *Circulation* 93:372-379.
- Yan GX, Antzelevitch C. 1999 “Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation.” *Circulation* 100:1660-1666.
- Zhang J, Sacher F, Hoffmayer K, O’Hara T, Strom M, Cuculich P, Silva J, Cooper D, Faddis M, Hocini M, Haïssaguerre M, Scheinman M, Rudy Y. 2015 “Cardiac electrophysiological substrate underlying the ECG phenotype and electrogram abnormalities in Brugada syndrome patients.” *Circulation* 131:1950-1959.
- Zipes DP, Wellens HJ. 1998 “Sudden cardiac death.” *Circulation* 98: 2334-2351.

Chapter 3

SUDDEN CARDIAC DEATH IN ATHLETES: REASONS AND PREVENTION

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ABSTRACT

Sudden death (SD) is the most dangerous and irreversible outcome of diseases in clinical as well as in sport medicine. Between 1980 and 2011, the Sudden Death in Young Athletes Registry in the United States, which was developed based on mass media information, recorded 2406 cases of sudden death, which were observed in 29 diverse sports. In the USA 80% of all SD occurred in high school/middle school or collegiate student athletes, 20% were engaged in organized youth, postgraduate.

Statistical data vary greatly in some regions: in the USA as 7.47 and 1.33 per 1,000,000 exercising male and female school-age athletes, respectively, whereas the SCD incidence rate in Italy, is 2.6 cases in men and 1.1 in women per 100,000 individuals per year that are involved in active competitive sports.

European Heart Rhythm Association (EHRA) position paper concluded that overall estimate, 1 to 2 out of 100 000 athletes between of age of 12 - 35 years old die suddenly each year. It was shown that the risk of SCD is significantly higher in athletes than in non-athletes with the same heart condition in the general population - by more than five times for ARVD/ARVC, 2.6 times for coronary artery disease, 1.5 times for myocarditis, and more than 2 times for cardiac conduction system diseases.

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INTRODUCTION

Sudden death (SD) is the most dangerous and irreversible outcome of diseases in clinical (Myerburg and Castellanos, 1971) as well as in sport medicine (Maron et al., 2006-2016; Corrado et al., 2005, 2006; Harmon et al., 2015; Finocchiaro et al., 2016). SD in the sports definition includes cases of death that occurred immediately during exercise as well as within the first 1 - 24 hours from the onset of initial symptoms that have led to a change or cessation of physical activity. SD in athletes mostly cases associated with sporting activity (Maron et al., 2016; Mont et al., 2017). In 2015 the European Guidelines for the Prevention of Sudden Death classified athletes into a separate group with a special risk of SD (Priory et al., 2015, 61).

SD is traditionally considered to be associated primarily with heart diseases. But according to the data provided by the US National Collegiate Athletic Association (NCAA) athletes between 2003 – 2013, accidents is the leading cause of death in the SD structure of athletes (50%), however the leading position among somatic diseases undoubtedly belongs to sudden cardiac death (SCD) which constitutes 15% of all SD cases; the other causes of SD, both medical and non-medical (suicide, homicide), do not exceed 10% (Harmon et al., 2015).

THE EPIDEMIOLOGY OF SCD IN SPORT

It is not easy to determine the accurate epidemiology of SCD in sport. Much depends on the selected inclusion criteria for the analysis, the age of the athletes, the level of athletic achievement, sporting experience, type of sport, and other factors. Therefore, studies carried out in different countries show an unequal SCD incidence rate in athletes. Between 1980 and 2011, the Sudden Death in Young Athletes Registry in the United States, which was developed based on mass media information, recorded 2406 cases of sudden death, which were observed in 29 divers sports (Maron et al., 2016). In this paper 80% SD occurred in high school/middle school or collegiate student athletes, 20% were engaged in organized youth, postgraduate.

SCD incidence rate determined in the USA as 7.47 and 1.33 per 1,000,000 exercising male and female school-age athletes, respectively (Van Camp et al., 1995). The statistical data can however vary greatly in some areas. According to (Corrado et al., 2005) the SCD incidence rate in Italy was 2.6 cases in men and 1.1 in women per 100,000 individuals per year that are involved in active competitive sports. In recent years, with screening of athletes before active exercise, this figure decreased to 0.87 cases per 100,000 per year. In the USA, in children and adolescent athletes, SCD is registered in 0.66 cases per 100,000 exercising male school students and 1.45 per 100,000 male

college students, and 0.12 per 100,000 female school students and 0.28 per 100,000 female college students, respectively (Van Camp et al., 1998). In Ireland (Quigley, 2000) the SCD incidence rate in sports was 1 case per 600,000, in a French study (Tabib et al., 1999) - 0.26 per 100,000 per year. In a study conducted on Rhoda Island (Ragosta et al., 1984), the rate was 0.36 per 100,000 per year in individuals aged up to 30 years and 4.46 and 0.05 per 100,000 per year in men and women older than 30, respectively. European Heart Rhythm Association (EHRA) position paper concluded that overall estimate, 1 to 2 out of 100 000 athletes between of age of 12 - 35 years old die suddenly each year (Mont et al., 2017, 43).

SCD AND TYPES OF SPORTS

The data on the sports associated with SCD cases as well as those on epidemiology are quite varied, depending on national sporting traditions, age, gender, and group inclusion criteria (professional sports, school sports, general fitness activity). In the USA (Maron et al., 2016) most SCD cases in young athletes in active competitive sports occurred in basketball and football (35 and 30%, respectively); soccer, cross country/track and baseball, accounted for 8%, 7% and 6% of the cases; such sports as wrestling, boxing, swimming, ice hockey, and marathon running, for between 5 and 1%, and rugby, triathlon, martial arts, tennis, volleyball, gymnastics, figure skating, golf and others, for less than 1%.

By other study from the USA (Harmon et al., 2016, 15) highest incidence SCD per athletes were 1 in 8978 in men's basketball, 1 in 23689 in men's soccer, 1 in 35951 in men's football. In a women it rate were 1 in 57611 in swimming and 1 in 77061 in basketball.

SCDs not associated with *Commotio cordis* (see below) were reported most frequently in children and adolescents involved in ice hockey, football, and basketball (Maron et al., 2009). In Spain SCD was observed most often in cyclists (34.4%), soccer players (21.3% in the general group and 33.3% in athletes younger than 35 years), and gymnasts (8%). Fewer deaths occurred in basketball, rowing, marathon running, jogging, and mountain climbing (Paz Suárez-Mier and Aguilera, 2002). In Italy (Corrado et al., 2005) the highest number of SCD cases was registered in soccer (40%), 9% of the cases - in swimming and rugby, 7% - in cycle racing, running and volleyball, and 3% of cases in judo, tennis, and gymnastics. It is clear that this rating of dangerous sports is based on a specific regional and temporal sample of published sports-related SCD cases and does not fully reflect all types of sports for which SCD were recorded. SCD cases associated with many other sports periodically come to public attention through the media. The studies by Quigley and Ragosta cited above most frequently recorded SCD when playing golf (31.3% and 23.4%, respectively), cricket (21.5%), and jogging, and less often during

basketball (10.2%), swimming (8%) and cycling races (6%). In a major study conducted in France (Marijon et al., 2011) SCD was most frequently observed during cycling (30.6%), jogging (21.3%), and soccer (13.05%) in individuals of all ages playing sports and exercising regularly SCD in other sports did not exceed 5% in this list.

COMMOTIO CORDIS

The SCD cases associated with a blunt blow to the heart area and classified as death caused by heart contusion (contusion cordis) or concussion (commotio cordis) constitute a special group (Strasburger and Maron, 2002; Maron et al., 2009; Bode F et al., 2006; Link MS et al., 2003). Occurring in the vulnerable phase of the cardiac cycle (the beginning of T-wave on ECG) this blow initiates fatal arrhythmias - ventricular fibrillation or at once asystole. Under normal heart rate (60-80 bpm), this vulnerable period takes up approximately 2-3% of the time, or up to 20% if the heart rate increases to 120 bpm or more. Therefore, athletes are more vulnerable to this grave complication during exercise. Young American athletes most frequently experience SCD in lacrosse, then hockey and basketball (Maron et al., 2009). There have been reports of SCD occurring from a punch to the heart in martial arts, due to being struck with a hockey puck or other circumstances. Commotio cordis is the cause of 2% (Harmon et al., 2015) to 20% (Maron et al., 2006, 2009, 2016) of SCD cases in young athletes.

GENDER AND AGE OF THE VICTIMS

According to the US Registry, the age of inclusion in the analysis of SCD and cardiac arrest in athletes was limited to 39 years, 2153 deaths from all causes (89%) occurred in males, and 253 deaths (11%) were in females (4). Mortality rate among the 842 athletes with autopsy-confirmed cardiovascular diagnoses, the incidence in males exceeded that in females by 6.5-fold, $P < .001$ (Maron et al. 2016, 1172). An analysis of 61 cases of SCD that occurred during exercise in Spain in 1995 to 2001 revealed that the age of the athletes and those involved in sport reached 65 years (mean age 31.9 ± 14.2 years). In 59 cases vs 2, the victims were male (Paz Suárez-Mier and Aguilera, 2002). Among 60 squash players who died suddenly at the age of 22 to 66 years (46 ± 10.3), 59 individuals (98.3%) were also male (Northcote et al., 1986). However, women may dominate in some sports characterized by a relatively small number of SCDs or cardiac arrests, e.g., 90% in volleyball, 73% in softball (Maron et al., 2016). The number of arrhythmias and SCD risk increase with age. However, this applies primarily to those who are not engaged in or who have retired from professional and competitive sport (Maron et al., 2016).

CIRCUMSTANCES OF SCD AND PRODROMAL SYMPTOMS

When analyzing the circumstances of SCD in young athletes, it was observed that in 83% of cases SCD occurred during or immediately after exercise and only 17% was not associated with any physical activity (Maron et al., 2016). In some cases, it was possible to obtain the medical histories of the victims or data on the presence of some specific diseases or conditions or potential symptoms preceding the fatal episode. In 60 squash players who died suddenly (Northcote et al., 1986) were performed an analysis of prodromal symptoms in. In a decreasing order of symptom frequency, athletes with sudden deaths complained of chest pain, increasing fatigue, non-specific gastrointestinal disorders, a burning sensation in the heart area, feeling short of breath, pain in the ears or neck, non-specific malaise, upper respiratory tract infections, dizziness and/or palpitations, and severe headache. Five of the victims (8.3%) had no significant symptoms before death. Prodromal symptoms were more frequent in athletes than in non-athletes of the same age who died suddenly, as observed by: 32% vs 23%, respectively (Corrado et al., 2003). This suggests that even minor, non-specific health complaints in regularly training athletes must be taken seriously by doctors, coaches, and the athletes themselves, as they may herald the onset of a life-threatening event. Some conditions in athletes, often considered to be undoubtedly life-threatening, such as syncope, to the contrary, are not always associated with a risk of sudden death, although that risk should always be ruled out first. For example, cardiac diseases with a high risk of SCD that required a withdrawal from the sport were revealed only in two (0.4%) of 474 young athletes with syncope (Golivicchi et al., 2004); these diseases were hypertrophic cardiomyopathy (HCM) in one case and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/ARVC) in the other. In our study (Makarov and Komoliatova, 2013), no diseases possessing a risk of SCD and requiring a withdrawal from sports have been identified in any of the 34 high-level athletes who had a history of syncope.

CAUSES OF SCD

Elucidation of the etiological causes of SCD in athletes is one of the most controversial issues in this area. Meanwhile, it is one of the key issues for the development of scientifically based methods for SCD prevention, selection of individuals suitable for sports, and primary and secondary prevention of SCD. Due to new technologies in diagnostics and an increasing number of studies in this area, the opinions on the etiology of SCD have changed considerably. In the 1980s, among all SCD cases in young athletes in the United States, HCM was diagnosed in 36% of athletes who died

suddenly, with the maximum left ventricular wall thickness from 15 mm to 40 mm (mean 23 ± 5 mm) and an average weight of the heart of 521 ± 113 g, followed by (in a descending order) coronary artery abnormalities, and borderline left ventricular hypertrophy, interpreted as possible HCM (Maron et al., 2016). However, we cannot exclude the possibility that it was exercise-induced cardiac hypertrophy (which is a component of the non-pathological athlete's heart), myocarditis, ARVD/ARVC, channelopathies (long or short QT syndrome, Brugada syndrome, idiopathic ventricular fibrillation, catecholaminergic ventricular tachycardia), i.e., diseases that can only be determined by an ECG prior to death. Other pathologies, such as mitral valve prolapse, aortic rupture, aortic stenosis, dilated cardiomyopathy, Wolff-Parkinson-White syndrome, rare non-specific myocardial damage (sarcoidosis), and other causes, were recorded in 1-2% of cases each.

A smaller (though with a more extended age range (11-65 years) analysis of sport-associated SCD cases in Spain (Paz and Aguilera, 2002) has demonstrated that in most cases the cause of SCD in all ages was ischemic heart disease (40.9%), arrhythmogenic cardiomyopathy (as in some cases there was not only right ventricular but biventricular dilatation, and this diagnosis was made) in 16.3% of cases, HCM (6.5%), left ventricular hypertrophy (4.9%), myocardial fibrosis (3.2%), coronary artery abnormalities (3.2%), dilated cardiomyopathy (1.6%), etc. In 16.3% of cases the cause of death remained unknown. When the observation group was divided into SCD cases occurring before and after 30 years of age, it was revealed that the majority of cases of ischemic heart disease were concentrated in the older age group (23 vs. 2 cases younger than 30 years), there was an equal number of cases of HCM, while ARVD/ARVC, coronary artery abnormalities, and all cases with uncertain autopsy results were more frequent among young individuals.

However, in the above-mentioned French study (Marijon et al., 2011) of SCD cases in athletes and persons regularly engaged in physical activity aged below 35 years, the percentage of HCM reached 10%, while cases classified as "unexplained death" accounted for 36%; according to the data from the US National Collegiate Athletic Association, published in 2015 (Harmon, et al., 2015), the structure of SCD included unexplained death (classified as sudden unexplained death - SUD) in 25% cases, confirmed HCM in 8%, and possibly HCM in 8%. The most up-to-date information on the subject is probably presented in the 2016 report by the British Registry of SCD in sports (Finocchiaro, et al., 2016), where SUD in all age categories constituted 42% and HCM, 6%. Marked changes in the age dynamics of SCD etiology were also noted. In the age group of over 35 years, SUD constituted 28% (idiopathic left ventricular hypertrophy with fibrosis - ILVHF, accounted for the same percentage); at the age of 18-35 years the proportion of SUD increased to 44% (ILVHF to 14%), and in the youngest group of <18 years, the frequency of SUD was the highest (56%), while ILVHF rates decreased to 10%. Rates of HCM and myocarditis confirmed by autopsy remained virtually unchanged

with age at 6 to 8% for HCM and 1-2% for myocarditis. The frequency of identified ARVD/ARVC moderately increased with age, from 6% in athletes under 18 years old to 14% at the age of 18 to 35 and 18% in athletes aged over 35 years.

ETHNIC DIFFERENCES

There are some ethnic differences in SCD rates depending on its cause. In general, over 27 years of observation in the United States, white males dominated in a large cohort of athletes who died suddenly (46%), followed by African Americans and other minority (43%), white and black and other minority females – 8% and 3% (Maron, et al., 2016). However, an analysis of specifically cardiovascular SCD in those who died from HCM and coronary artery abnormalities revealed significantly higher (more than two-fold) rates in African Americans, while Caucasians were still at the top of the list for ARVD/ARVC and primary electrical diseases (channelopathy). In the European study (Corrado, et al., 2003), the range of diseases identified in athletes suddenly dying was almost the same, yet there were significant differences in the frequency of the main variants of myocardial damage - ARVD/ARVC was detected in 24% of cases, HCM in 2%, and myocarditis in 10%. If the proportion of the three major variants of myocardial damage (ARVD/ARVC, HCM, and myocarditis), detected in suddenly dying young American and Italian athletes, is compared, similar aggregate values are obtained, namely 38% in Italy and 46% in the USA. Taking into account all potential ethnic differences or autopsy reports, there may be a different interpretation of similar pathomorphological changes.

Nevertheless, it is obvious that the main risk group for SCD in athletes includes those with life-threatening cardiac arrhythmias and myocardial changes. However, the risk of SCD is significantly higher in athletes than in non-athletes with the same heart condition in the general population - by more than five times for ARVD/ARVC, 2.6 times for coronary artery disease, 1.5 times for myocarditis, and more than 2 times for cardiac conduction system diseases (Maron, et al., 2016).

SCD PREVENTION IN ATHLETES

Solutions to this problem vary from country to country. In the USA, a group of American Heart Association (AHA) experts has proposed 12 steps that can help in the prevention of SCD in athletes at the initial screening stage (Maron, et al., 2007). These include the following conditions and medical history features:

Medical history

1. Chest pain/discomfort on exertion.
2. Sudden fainting/presyncope.
3. Vertigo (dizziness) on exertion.
4. Heart murmurs.
5. High blood pressure (> 140/90 or more on the first measurement).

Family History

6. Sudden death of relatives aged under 50 years.
7. Cardiovascular disease in close relatives under 50 years.
8. Cardiomyopathy, LQTS, Marfan syndrome, ARVD/ARVC or other conditions with a risk of life-threatening arrhythmias or coronary artery disease in relatives.

Physical Examination

9. Femoral pulse.
10. Marfan syndrome manifestations.
11. Sitting BP measurements.

It is noteworthy that an ECG is not included in this screening list. Supporting this approach, the guideline authors note that the rates of SCD in athletes in the United States and Italy (where an ECG is a compulsory component of the medical checkup in athletes before training) are about the same. A prospective cohort study in individuals aged below 36 years engaged in competitive sports was conducted in the Italian region of Veneto between 1979 and 1999. The most frequent cause of SCD in the study was ARVD/ARVC (24%), followed by ischemic heart disease of atherosclerotic etiology (20%), abnormal outlet of coronary arteries (14%), and mitral valve prolapse (12%) (Corrado, et al., 2006). Among older athletes (> 35-40 years), more than half of the cases of SCD were associated with ischemic heart disease, as in the general population.

Some other American studies support the use of an ECG as part of a medical checkup of athletes at the early stages. A large study of 5,615 young athletes conducted in Nevada (USA) demonstrated that the sensitivity of an ECG in the identification of serious cardiovascular pathology was 70% compared to 3% in the group of athletes where only a medical history and physical examination were used (Fuller, et al., 1997). The specificity of ECG was 97.4%. Only 0.4% (22 of 5,615) were withdrawn from sporting competitions. The estimated 'cost' of a life saved by using only clinical and medical history data in this study was USD 84,000, while by adding an ECG it may be reduced almost two-fold (USD 44,000).

In the Japanese study (Tanaka, et al., 2006), the researchers evaluated ECG screening results in 68,503 school students, and the SCD incidence in adolescents involved in competitive sports was on average 1.32 per 100,000 per year. Three deaths occurred in children without preceding syncope or SCD cases in the family history. In one 14-year-

old boy, HCM had been identified earlier, at the pre-screening stage, and he was withdrawn from the sport, but he still died suddenly while jogging. In two other cases (13- and 16-year-old boys), SCD occurred while playing handball and basketball, and both had a normal ECG and no pathological changes identified during autopsy. The estimated 'cost' of a life saved by using ECG screening in this study was USD 8,000 (26).

Together with history and physical examination the mandatory instrumental part of the cardiac examination in members of Russian junior national teams (less 18 years old), consist of a 12-lead resting ECG (with using original normal ECG criteria, which were elaborated at 500 young elite athletes (Makarov, et al. 2013), EchoCG, and bicycle ergometry or treadmill test. A more thorough examination (Holter monitoring, analysis of heart rate turbulence, ventricular late potentials, magnetic resonance therapy, tilt-test, etc.) depends on the changes detected at the preliminary stage, as well as medical history features, such as syncope, sudden death in the family, ECG changes, etc.

Despite a rather sizable document, it seems to us that for so-called elite athletes in high-level sports it would be beneficial to include Holter monitoring, for special indication in athletes with syncope, arrhythmias, palpitation, pathological changes of ECG - long or short QT and other (Makarov, et al. 2015).

The European experience, which formed the basis for the International Olympic Committee recommendations, includes gathering a detailed medical history with an emphasis placed on the identification of complaints of potentially arrhythmogenic origin (palpitations, heart pain, etc.), syncope, cardiovascular disease and cases of SCD in the family, especially at a young (under 50 years) age, and physical and ECG examinations, especially focusing on abnormal heart murmurs, alterations in blood pressure, ECG criteria of heart chamber hypertrophy, signs of myocardial ischemia, shortening or lengthening of the QT and PR intervals, and ventricular and supraventricular tachyarrhythmias (Corrado, et al., 2006). The use of such screening, including an ECG in assessing the risk of SCD for 25 years in Italy has shown that the incidence of SCD in young athletes aged 12-35 years engaged in competitive sports declined from 3.6 SCD cases per 100,000 per year (one death per 27,777 athletes) in 1979-1981 to 0.4 deaths per 100,000 per year (one death per 250,000 athletes) in 2003-2004. In general, SCD in athletes included in the screening decreased by 89%, whereas the incidence of SCD in the population not covered by the screening has not changed during the period (Corrado, et al., 2006). This was due primarily to an increase in early detection and withdrawal from competitive sports of young people suffering from HCM, ARVD/ARVC, and dilated cardiomyopathy (from 4.4% in 1979 to 9.4% in 2004). ECG changes may be the only early marker of a risk of life-threatening arrhythmias and SCD in athletes. However, the interpretation of ECG in athletes has its own peculiarities; any potentially life-threatening changes may be affected by conditions specific only to sports. For instance, the QT interval is longer in athletes (Moss, 2007), its shortening was revealed when using some anabolic agents in athleticism (Ali Babae Bigi, et al., 2009). The emergence of new,

non-invasive methods of electrocardiological diagnostics seems to be promising for risk group stratification in sports. Certain features of the QT interval frequency adaptation (Genovesi, et al., 2007) and microvolt T-wave alternans (Madias, et al., 2008; Inama, et al., 2008) may aid in the stratification of athletes with electrical instability of the heart and an increased risk of life-threatening arrhythmias and SCD, and they may differentiate pathological and non-pathological transformations of the athlete's heart.

Prevention of sudden cardiac death in athletes ESC

Recommendations	Class ^a	Level ^b	Ref ^c
Careful history taking to uncover underlying cardiovascular disease, rhythm disorder, syncopal episodes or family history of SCD is recommended in athletes.	I	C	This panel of experts
Upon identification of ECG abnormalities suggestive of structural heart disease, echocardiography and/or CMR imaging is recommended.	I	C	This panel of experts
Upon identification of ECG abnormalities suggestive of structural heart disease, echocardiography and/or CMR imaging is recommended.	IIa	C	This panel of experts
Physical examination and resting 12-lead ECG should be considered for pre-participation screening in younger athletes.	IIa	C	This panel of experts
Middle-aged individuals engaging in high-intensity exercise should be screened with history, physical examination, SCORE and resting ECG.	IIa	C	Nolan, et al., 2010
Staff at sporting facilities should be trained in cardiopulmonary resuscitation and on the appropriate use of automatic external defibrillators.	IIa	C	Borjesson et al., 2011; Menafoglio et al., 2014

CMR = cardiac magnetic resonance; ECG = electrocardiogram; SCD = sudden cardiac death; SCORE = Systematic Coronary Risk Evaluation (39).

a = Class of recommendation.

B = Level of evidence. C = Reference(s) supporting recommendations.

The main fatal arrhythmia leading to death is ventricular fibrillation. If this develops, the most effective method for treatment is electric defibrillation. As was shown above, the majority of SCD cases in athletes occur during engagement in sport (Maron, et al., 2016; Corrado, et al., 2006), in contrast to similar data from non-athletes where up to 80% of SCD cases are registered at home (Makarov, et al., 2015). This enables the

creation of a system of more effective medical aid in the first few minutes after cardiac arrest during physical activity. According to the U.S. National Registry of Sudden Death, in cases of sudden death associated with exercise in young people over the period from 2000 and 2006, the percentage of survival in the latter three years of the study almost doubled compared to the first three years, reaching 14-17% (Drezner, et al., 2008). And only in 2006 similar rates of successful recovery after cardiac arrest were achieved by using automatic external defibrillators (AED), which are publicly available, and electrical defibrillation performed by specialized emergency teams (Drezner, et al., 2008). There were many reports of successful defibrillation in cardiac arrest in athletes during physical activity or competition (Strasburger and Maron, 2002).

The 2015 European Society of Cardiology Guidelines for the prevention of SCD propose the following algorithm of SCD prevention in athletes (Priory et al. 2015, 61):

It was also evaluated labor costs, effectiveness and economic costs of comprehensive preventive screening in 785 athletes aged 5 to 65 years who are engaged in high-intensity sports (Menafoglio et al., 2014). As a result of this screening, newly diagnosed cardiovascular diseases were identified in 2.8% of athletes; economic costs were USD 199 per athlete. The researchers consider such a screening to be warranted and affordable. The guidelines also highlight the importance of training coaches and staff in sports centers on the actions needed in case of emergency, performing cardiopulmonary resuscitation and the use of AED, both in athletes and spectators during major competitions (Borjesson et al., 2011).

REFERENCES

- Ali Babae Bigi, Mohammad., Aslani, Amir and Aslani, Arsalan. 2009. Short QT Interval: A Novel Predictor of Androgen Abuse in Strength Trained Athletes. *Ann Noninvasive Electrocardiol.* 4(1):35–9.
- Bode, Frank., Franz, Michael., Wilke, Iris., Bonnemeier, Hendrik., Schunkert, Ytribert., Wiegand, Uwe K.H. 2006. Ventricular fibrillation induced by stretch pulse: implications for sudden death due to commotio cordis. *J Cardiovasc Electrophysiol.* 17: 1011-7, 2006. DOI: 10.1111/j.1540-8167.2006.00547.x.
- Borjesson, Mats., Luis Serratos, Francois, Carre., Corrado, Domenico., Drezner, Domenico., Dugmore, Dorian L., Heidbuchel, Hein H., Mellwig, Klaus-Peter., Panhuyzen-Goedkoop, Nicole M., Papadakis, Michael., Rasmussen, Hanne., Sharma, Sanjay., Solberg, Erik E., van Buuren, Frank., Pelliccia, Antonio. 2011. Consensus document regarding cardiovascular safety at sports arenas: position stand from the European Association of Cardiovascular Prevention and Rehabilitation (EACPR), section of Sports Cardiology. *European Heart Journal* 32:2119-24.

- Colivicchi, Furio., Ammirati, Fabrizio., Santini, Massimo. 2004. Epidemiology and prognostic implications of syncope in young competing athletes. *European Heart Journal*. 25(19):1749-53.
- Corrado, Domenico., Basso, Cristina., Pavei, Andrea., Michieli, Pierantonio., Schiavon, Maurizio., Thiene, Gaetano. 2006. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA*. 296:1593—601.
- Corrado, Domenico., Basso, Cristina., Rizzoli, Giulio., Schiavon, Maurizio., Thiene, Gaetano. 2003. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol*. 3;42(11):1959-63.
- Corrado, Domenico., Pelliccia, Antonio., Halvor Bjørnstad, Hans., Vanhees, Luc., Biffi, Alessandro., Borjesson, Mats., Panhuyzen-Goedkoop, Nicole., Deligiannis, Asterios., Solberg, Erik., Dugmore, Dorian., Mellwig, Klaus P., Assanelli, Deodato., Delise, Pietro., van-Buuren, Frank., Anastasakis, Aris., Heidbuchel, Hein., Hoffmann, Ellen., Fagard, Robert., Priori, Silvia G., Basso, Cristina., Arbustini, Eloisa., Blomstrom-Lundqvist, Carina., McKenna, William J. and Thiene, Gaetano. 2005. Cardiovascular preparticipation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. *European Heart Journal*, 26:516–24. DOI:10.1093/eurheartj/ehi108.
- Drezner, Jonathan A., Chun, Jordan S.D.Y., Harmon, Kimberly G., Derminer, Linette. 2008. Survival trends in the United States following exercise-related sudden cardiac arrest in the youth: 2000—2006. *Heart Rhythm* 2008; 5: 794–9.
- Finocchiaro, Gherardo., Papadakis, Michael., Robertus, Jan-Lukas., Dhutia, Harshil., Klavdios Steriotis, Alexandros., Tome, Maite., Mellor, Greg., Merghani, Ahmed., Malhotra, Aneil., Behr, Elijah., Sharma, Sanya., Sheppard, Marry N. 2016. Etiology of Sudden Death in Sports: Insights from a United Kingdom Regional Registry. *J Am Coll Cardiol*. 10;67(18):2108-15. doi: 10.1016/j.jacc.2016.02.062.
- Fuller, Colin M., McNulty, Candace V., Spring, Donald A., Arger, Rosta m., Bruce, Stephen S., Chrysos, Basil E., Drummer, Eric M., Kelley, Frank P., Newmark, Michael J., Whipple, Gerald H. 1997. Prospective screening of 5,615 high school athletes for risk of sudden cardiac death. *Medicine & Science in Sports & Exercise*. 29:1131–8.
- Genovesi, Simonetts., Zaccaria, Daniele., Rossi Emanuela., Grazia Valsecchi, Maria., Stella, Andrea., Stramba-Badiale, Marco. 2007. Effects of exercise training on heart rate and QT interval in healthy young individuals: are there gender differences? *Europace*. 9, 55–60.
- Harmon, Kimberly, G., Asif, Irfan M., Maleszewski, Joseph J., Owens, David S., Prutkin, Jordan M., Salerno, Jack C., Zigman, Monica L., Ellenbogen, Rachel., Rao, Ashwin L. Ackerman, Michael J., Drezner, Jonathan A. 2015. Incidence, Cause, and Comparative Frequency of Sudden Cardiac Death in National Collegiate Athletic

- Association Athletes A Decade in Review. *Circulation*. 132:10-9. DOI: 10.1161/CIRCULATIONAHA.115.015431.
- Inama, Giuseppe., Pedrinazzi, Claudio., Durin, Ornella., Nanetti, Massimiliano., Donato, Giorgio., Pizzi, Rita., Assanelli, Deodato. 2008. Microvolt T-wave alternans for risk stratification in athletes with ventricular arrhythmias: Correlation with programmed ventricular stimulation. *Ann Noninvasive Electrocardiol*. 13:14–21. doi: 10.1111/j.1542-474X.2007.00196.x.
- Link, Mark S., Maron, Barry J., Wang, Paul J., VanderBrink, BA, Zhu, Wei., Estes, Mark N.A.III.2003. Upper and lower limits of vulnerability to sudden arrhythmic death with chest-wall impact (commotio cordis). *J Am Coll Cardiol*. 41: 99-104.
- Madias, John E. 2008. Athletes, ventricular arrhythmias, electrophysiological testing, microvolt T-wave alternans, and a follow-up of 30 ± 21 months: A need for follow-up updates. *Ann Noninvasive Electrocardiol*. 13:319–20.
- Makarov, Leonid., Komoliatova, Vera. 2013. Syncope in the young elite athletes. *European Heart Journal*, Vol. 34, Issue suppl 1, P 1363. DOI: <http://dx.doi.org/10.1093/eurheartj/eh308.P1363>.
- Makarov, Leonid., Komoliatova, Vera., Kiseleva, Irina., Fedina, Natalia., Besportochny, Dmitryi. 2015. The role of Holter monitoring in the examination of young elite athletes. *The European Journal of Preventive Cardiology*. 22: S126 doi:10.1177/2047487315586744.
- Makarov, Leonid., Komoliatova, Vera., Kolosov, Vlad., Fedina, Natalia., Kiseleva, Irina. 2013. The peculiarity of the rest electrocardiograms in young elite athletes. *The European Journal of Preventive Cardiology*.20; Suppl. 1 2013.
- Makarov, Leonid., Komoliatova, Vera., Fedina, Natalia and Solokhin Yuri. 2015. Prevalence of Out-of-Hospital Sudden Cardiac Death in Moscow in 2005–2009. *Advances in Epidemiology*, Article ID 310878, 6 pages, 2015. doi:10.1155/2015/310878.
- Marijon, Eloi., Tafflet, Muriel., Celermajer, David S., Dumas, Florence., Perier, Marie-Cecile., Mustafic, Hazrije., Toussaint, Jean-Francois., Desnos, Michel., Rieu, Michel., Benameur, Nordine., Le Heuzey, Jean-Yves., Empana, Jean-Philippe., Jouven, Xavier. 2011. Sports-Related Sudden Death in the General Population *Circulation*.124:672-681.doi:10.1161/CIRCULATIONAHA.110.008979.
- Maron, Barry J., Haas, Tammy S., Ahluwalia, Aneesha., Murphy, Caleb J., Garberich, Ross F. 2016. Demographics and Epidemiology of Sudden Deaths in Young Competitive Athletes: From the United States National Registry. *The American Journal of Medicine*. 129, 1170-7. <http://dx.doi.org/10.1016/j.amjmed.2016.02.031>.
- Maron, Barry J., Pelliccia, Antonio. 2006. The Heart of Trained Athletes: Cardiac Remodeling and the Risks of Sports, Including Sudden Death. *Circulation*. 114:1633-44.

- Maron, Barry J., Thompson, Paul D., Ackerman, Michael J., Balady, Gary., Berger, Stuart., Cohen, David., Dimeff, Robert., Douglas, Pamela S., Glover, David W., Hutter, Adolph M., Krauss, Michael D., Maron, Martin S., Mitten, Matthew J., Roberts, William O., Puffer, James C. 2007. American Heart Association Council on Nutrition, Physical Activity, and Metabolism Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 27;115(12):1643—455.
- Maron, Barry J., Doerer, Joseph J. Tammy, S. Haas., Estes, N.A. Mark N.A., Hodges, James S., Link, Mark S. 2009. Commotio cordis and Epidemiology of Sudden Death in competitive Lacrosse. *Pediatrics*; 124(3): 966-971 doi: 10.1542/peds.2009-0167.
- Menafoglio, Andrea., Di Valentino, Marcelli., Porretta, Alessandra Pia., Foglia, Pietro., Segatto, Jeanne-Marie., Siragusa, Patrick, Pezzoli, Reto., Maggi, Mattia., Romano, Gian Antonio, Moschovitis, Giorgio., Gallino Augusto. 2014. Cardiovascular evaluation of middle-aged individuals engaged in high-intensity sport activities: implications for workload, yield and economic costs. *Brit J Sports Med*. 49:757-61. 13. doi:10.1136/ bjsports-2014-093857.
- Mont, Luis., Pelliccia, Antonio., Sharma, Sanjay., Biffi, Alessandro., Borjesson, Mats., Brugada Terradellas, Josep., Carre, Francois., Guasch., Eduard., Heidbuchel, Hein., La Gerche, Andre., Lampert, Rachel., McKenna, William., Papadakis, Michail., Priori, Silvia G., Scanavacca, Mauricio., Thompson, Paul., Sticherling, Christian., Viskin, Sami., Wilson, Mathew and Corrado, Domenico. 2017. Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. *European Journal of Preventive Cardiology*. 24(1) 41–69. DOI: 10.1177/2047487316676042.
- Moss, Arthur J. What duration of the QTc interval athletes from competitive sports? 2007. *European Heart Journal*. 28, 2825–6.
- Myerburg Robert J., and Castellanos Agustin. 1997. "Cardiac arrest and sudden cardiac death". In *Heart disease: a textbook of cardiovascular medicine*, edited by Braunwald, Eugene, 742–79, New York: WB Saunders Publishing Co.
- Nolan, Jerry P., Soar, Jasmeet., Zideman, David A., Biarent, Dominique., Bossaert, Leo L., Deakin, Charles., Koster, Rudolf W., Wyllie, Johnatan., Bottiger, Bernd. 2010. Group ERCGW. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation*. 81: 1219-76. DOI: <http://dx.doi.org/10.1016/j.resuscitation.2010.08.021>.
- Northcote, Robin., Flannigan, Clare., Ballantyne, David. 1986. Sudden death and vigorous exercise--a study of 60 deaths associated with squash. *Brit Heart Journal*. 55(2): 198–203.

- Paz, Suárez-Mier M. and Aguilera Beatriz. 2002. Causes of sudden death during sports activities in Spain. *Rev Esp Cardiol*. 55(4):347-58.
- Priori, Silvia G., Blomstrom-Lundqvist, Carina., Mazzanti, Andrea., Blom, Nico., Borggrefe, Martin., Camm John., Elliott, Perry Mark., Fitzsimons, Donna., Hatala, Robert., Hindricks, Gerhard., Kirchhof, Paulus., Kjeldsen, Keld., Kuck, Karl-Heinz., Hernandez-Madrid, Antonio., Nikolaou, Nikolaos., Norekva, Tone M., Spaulding, Christian., and Van Veldhuisen, Dirk J. 2015. ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *European Heart Journal*, 1;36 (41): 2793-867. doi:10.1093/eurheartj/ehv316.
- Quigley, Fionnuala. 2000. A survey of the causes of sudden death in sport in the Republic of Ireland. *Brit J Sports Med*, 34:258-61.
- Ragosta, Mikhael., Crabtree Jeannie., Sturner, William Q., Thompson, Paul D. Death during recreational exercise in the state of Rhode Island. *Med Sci Sports Exerc* 1984;16:339-42.
- Strasburger, Janette., Maron, Barry J. 2002. Commotio Cordis. *New England Journal Medicine*, 347 (16) 17.
- Tabib, A., Miras., A, Taniere P., Loire R. 1999. Undetected cardiac lesions cause unexpected sudden cardiac death during occasional sport activity. A report on 80 cases. *European Heart Journal*, 20:900-3. DOI: 10.1053/euhj.1998.1403.
- Tanaka, Yui., Yoshinaga, Masao., Anan, Ryuichiro., Tanaka, Yasuhiro., Nomura, Yuichi., Oku, Shozo., Nishi, Seiji., Kawano, Yoshifum., Tei, Chuwa., Arima, Katsura. 2006. Usefulness and cost effectiveness of cardiovascular screening of young adolescents. *Medicine & Science in Sports & Exercise*. 38:2– 6.
- Van Camp, Steven P., Colin, Bloor M., Mueller, Frederick O., Cantu, Robert C., Olson, Harold G. 1995. Nontraumatic sports death in high school and college athletes. *Medicine & Science in Sports & Exercise*: 27(5):641-7.

Chapter 4

SUDDEN CARDIAC DEATH IN ATHLETES: EPIDEMIOLOGY, ETIOLOGY, AND ESSENTIALS

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ABSTRACT

The words “exercise” and “athlete” usually evoke the concepts of “health” and “strength” for most of people throughout the world. It has also been reported that regular exercise can increase longevity. But sudden cardiac death (SCD) in athletes creates a great challenge on the beneficial effects of exercise training. The unexpected death of young athletes on sports fields generates widespread public and media attention and also raises a vital question: Is exercise really fatal? Sudden and asymptomatic deaths are tragic and usually produce adverse effects. These complications can be truly magnified by the death of an elite and famous athlete. The incidence of SCD is observed in athletes more frequently than non-athlete people and the victims are found oftentimes among males. Exercise is obviously not a killer per se. It can even reduce death risk by diminishing the cardiovascular risk factors. However, adverse cardiovascular effects of excessive intensive training and chronic exposure to very long distance races should not be overlooked. Exercise can be fatal in the presence of latent underlying heart disease. Of course, in certain circumstances such as exhaustive competitions. Both genetic and acquired conditions are associated with the etiology of SCD in athletes. The genetic structure of hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy/ dysplasia diseases is the most common cause of SCD in young athletes (<35 years of age). But acquired coronary artery disease is considered as the main cause of SCD in older athletes (>35 or 40 years). Ergogenic aids are also raised as a possible cause of problematic etiology of SCD in athletes. Exercise-induced physiological cardiac hypertrophy, also known as athlete’s heart, is an adaptive response and does not

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constitute a risk factor for SCD event. The systematic screening as a primary strategy along with resuscitation attempts as a secondary strategy, are significantly effective in prevention and improvement of the survival, respectively.

Keywords: cardiac death, athlete's heart, pathology, cardiac screening, sport

INTRODUCTION

The news of sudden cardiac death (SCD) of anyone, anywhere on the planet is indeed tragic, and it could leave complex social and psychological consequences, particularly when this unexpected event occurs in the total absence of any symptom and warning beforehand. When athletes fall victim to SCD, it may raise many controversies; firstly, it is found unbelieving by most of the people and secondly, it excites more heart-felt sympathy and passion since the victims are often young athletes who are always thought as the symbols of health (Maron, 2003) and thus less likely to be victims of heart attacks. More accurately, although health benefits of exercise training for the prevention of cardiovascular disorder have been well-documented (De Backer, et al., 2003), the incidence of SCD in athletes often during sport competitions and training programs, or even sometimes at rest times, cancels out all benefits of exercise training noted so far (Maron, et al., 2009, Chandra, et al., 2013). It has been shown that the risk of SCD among competitive athletes is approximately 2.8 times higher than non-athletic controls (Van Camp, et al., 1995). Therefore, exercise or sports-related activities may be like a double-edged sword: it can be a protector (individuals with a regular exercise program) or a trigger (individuals with latent heart diseases) for sudden death (Thiene, et al., 2010). The mechanisms of exercise-induced-SCD are complicated and ambiguous to some extents. Exercise training promotes certain morphological and functional adaptations in the heart-known as athlete's heart (Garcia and Costa, 2011). These changes are usually benign and reversible (Garcia and Costa, 2011). Nevertheless, chronic excessive endurance exercise may increase the risk of adverse structural remodeling in the heart and large arthritis (Patil, et al., 2012). Increase in the homogeneity of depolarization sometimes may cause risk of arrhythmias and SCD; the alterations of this factor was influenced by variables such as cardiac hypertrophy (athlete's heart) and/or hypertrophic cardiomyopathy (HCM), enhanced sympathetic tone, genetic disorders, use of medications, doping agents or food ingredients (Varró and Baczkó, 2010). Ventricular arrhythmia is commonly considered as an SCD mechanism and exercise may act on the arrhythmogenic substrate by triggering the release of catecholamines (Chandra, et al., 2013). It should be noted that intense exercise can cause another type of arrhythmias (atrial fibrillation) in mice via tumor necrosis factor alpha (TNF- α) -dependent inflammatory response (Aschar-Sobbi, et al., 2015). Moreover, exercise-induced SCD

may be influenced by accessory factors such as dehydration, hyperpyrexia, electrolyte imbalances, and increased platelet aggregation associated with exercise (Sharma, 2003). It is noteworthy that exercise-induced SCD can probably come from the interaction of high-intensity exercise with underlying cardiovascular disorders (Corrado, et al., 2003).

It must be acknowledged that SCD in athletes is an inevitable truth, and it still remains a major challenge for cardiovascular specialists involved with athletes (Corrado, Basso, et al., 2006, Fazelifar, et al., 2009). The media usually amplifies the mournful impact of this tragedy for the family of the dead athletes and as well for the whole community (Sweeting, et al., 2016). Because of the emotional nature of this phenomenon and the fact that it may discourage people from participating in sports and exercise programs, a scientific understanding of the details, etiology, and preventive strategies to reduce the incidence of SCD in young athletes seems quite vital. The author believes that an accurate cardiovascular evaluation of athletes during the preparation phases, and in the days before the competition is a rational strategy to minimize the risk of SCD in this population. This chapter summarizes the literature regarding the SCD in athletes with focus on the educational and practical approaches.

THE CONCEPT OF SCD

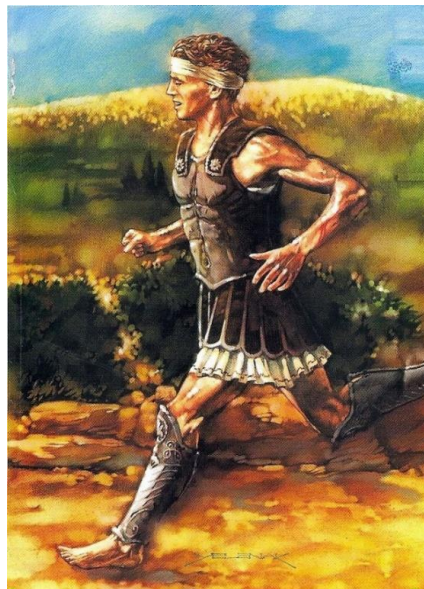
The term “athlete” escapes an exact definition; an athlete may be defined as a person (of any age) who, for excellence and achievement in official sport competitions (individual or collective), participates in systematic preparation phases and exhaustive workouts (Pelliccia, Fagard, et al., 2005, Owøye, 2010). The amount of exercise training per week determines whether an athlete is competitive or non-competitive (recreational athletes). An important feature of competitive athletes is doing exercise for more than 10 hours per week, whereas the amount of weekly training for recreational athletes is less than 10 hours (Solberg, et al., 2016). Various definitions are given by different organizations and cardiovascular researchers while investigating the concept of SCD, that each in turn may affect the precise prevalence of this phenomenon in the athlete population (Amital, et al., 2004). American College of Cardiology (ACC) describes this phenomenon as a non-traumatic and unexpected sudden death probably caused by cardiac arrest that may occur within 6 hours of a previously normal state of health (Maron, et al., 2005).

According to World Health Organization (WHO), SCD is a condition which arises within the first 24 hours after the onset of symptoms, while a group of experts decreased this period of time and defined it as a sudden and unexpected death, characterized by an abrupt loss of consciousness within the first hour after the symptom's onset in the presence or absence of cardiovascular abnormalities (Amsterdam, 1990). However, the definition provided by the WHO should not be considered as SCD because the relevant

definition encompasses many cases of well-established acute myocardial infarction (Virmani, et al., 2001). SCD of athletes or sport-related SCD is defined as a non-traumatic event that may occur during or within 1 hour after exercise with intensity of moderate to high in a competitive athlete (Holst, et al., 2010). If this event occurs during a heavy competition (high physiological and psychological needs), the deceased (man or woman) is considered as a competitive athlete (Holst, et al., 2010).

THE LEGEND OF SCD IN ATHLETES

The first unexpected sudden death of an athlete occurred in 490 BC; In fact, the first and the most tragic sudden death was recorded for a 40-year-old athlete (a veteran long-distance runner or messenger) and of course hero, namely Pheidippides (following picture) (Rich, 1994). During the Greco-Persian War (490 BC), Pheidippides was forced to run approximately 26 miles (40 km) to convey an important and auspicious message to the people of Athens. Upon arrival to the Athens, he fell dead immediately after reporting the defeat of the Persians army (according to legend: he exclaimed “victory is ours” then died) (Patil, et al., 2012). The death of famous athletes has brought public consciousness on the SCD. Some of the athletes who died due to SCD are as follows (Koester, 2001): Jim Fixx (marathon runner-1984), Flo Hyman (Olympic volleyball player-1986), Pete Maravich (former basketball star-1988), Hank Gathers (college basketball star-1990), Reggie Lewis (professional basketball All-Star-1993), and Sergei Grinkov (Olympic figure skating Champion 1995). Another outstanding figure, Micah True, also known as Caballo Blanco (white horse), was the mythic long-distance runner (born to run book:



Christopher McDougall, Knopf Publishing, 2009) who fell victim to the unwelcomed SCD. This legendary ultra-marathoner (Micah True used to run as far as 100 miles in a day) died suddenly during his routine running program (about 12-miles) on March 27, 2012 (Patil, et al., 2012). Enlargement and lesion of his heart significantly had been confirmed by autopsy. It seems that Micah's death had been a result of fatal arrhythmias (O'Keefe, et al., 2011). Pathological changes of Micah and Pheidippides' heart were approximately the same, namely cardiomyopathy manifestations; cardiomyopathy disorder may occur as a result of chronic excessive endurance exercise (Trivax and McCullough, 2012).

EPIDEMIOLOGY OF SCD IN ATHLETES

The incidence of SCD in both ordinary people and athletes is affected by several factors such as age and gender, ethnicity, nationality, screening procedures in the diagnosis of sudden death, prevention strategies, and definitions used for it (Holst, et al., 2010). The incidence of SCD in athletes is controversial for various reasons such as specific differences in the methodology of the conducted studies. Generally, the risk of SCD induced by training programs and heavy competition for athletes has increased about 2.8 times in comparison with non-competitive counterparts (Van Camp, et al., 1995). SCD is considered as one of the most common medical causes of death in athletes; the incidence rates of SCD are different (approximately from 1 per 3000 to 1 per 917, 000) depending on the ethnicity and type of sport or exercise (Harmon, et al., 2014). The incidence of SCD in male athletes is significantly higher (5-fold) than female athletes (Van Camp, et al., 1995). This disparity of death rate between the two genders can be explained by the possible confounding factors like low participation of women athletes in professional sports and lower prevalence rates of cardiac disorders that, by itself, affects the occurrence of SCD in the women involved in training and competition (Pelliccia, et al., 1996). In other words, incidence rates of SCD trigger factors such as cardiomyopathies (Miura, et al., 2002) and premature coronary artery disease (CAD) (Corrado, et al., 1994) is substantially higher in men than women. Age may also play a role in the incidence rates of SCD associated with exercise. It can increase the incidence of the SCD because athletes aged 36-49 years have experienced a higher incidence rate of SCD than athlete aged 12-35 years (6.64 per 100, 000 athlete [per year] versus 0.47 per 100,000 athlete, respectively) (Risgaard, et al., 2014). Interestingly, this study also reveals that there is no statistically significant difference in incidence rates of SCD between competitive and non-competitive (recreational) athletes and that the rate of SCD associated with sports is much lower than SCD in those who do not exercise or general population (incidence rate: 10.7 per 100, 000 people per year). A higher incidence rate of SCD has been reported in Italian athletes (competitive athletes, age 14-35 years) compared with US athletes (high school and college athletes, age 12-24 years) (Corrado,

Basso, et al., 2006, Van Camp, et al., 1995). Higher rate of SCD in Italian athletes may be due to a higher age range of participants and their exercise levels or further experience of training. In addition, the rate of SCD among African American athletes is approximately 5 times higher than white athletes (Maron, et al., 2014). This difference may be attributed to the higher prevalence of heart failure (Sharma, et al., 2014) and hypertension (Fuchs, 2011) in African Americans compared with the whites. The role of cardiomyopathy has been repeatedly confirmed as a central mechanism involved in the incidence of SCD in young athletes and the rate of death associated with HCM in black athletes is higher than white athletes (20% vs. 10%, respectively) (Maron, et al., 2009). The incidence rates of SCD are greater in some sports. In the US, basketball and football players, and in Europe, soccer athletes are often victims of this horrific event (Maron, Shirani, et al., 1996). Taken together, it seems that athletes involved in sports with the characteristics of high dynamic and low isometric intensity are at higher risk of SCD (Chandra, et al., 2013).

ETIOLOGY (COMMON CAUSES) OF SCD IN ATHLETES

Several causes are associated with the incidence of SCD in athletes. According to Reisdorff and Proding (Reisdorff and Proding, 1998) more than 20 pathological factors are involved in the SCD of young athletes. However, only a few of them are predominant and play a key role in the occurrence of SCD. It seems that HCM is more predominant (responsible for about 24% of deaths) than the coronary artery disorders (responsible for about 19% of deaths) in the pathogenesis of SCD in athletes (McCaffrey, et al., 1991). According to Maron et al. (Maron, Shirani, et al., 1996), HCM is associated with all the deaths about 46%. Other studies also confirmed the predominant role of HCM as the cause of SCD (responsible for almost half of all deaths) (Maron, et al., 1982, Maron, et al., 1980). The causes of SCD in athletes have been classified into acquiring and genetic risk factors, by Joanna and Christopher (Sweeting and Semsarian, 2016): myocarditis and CAD are considered as the acquired causes of SCD in athletes. Genetic causes also known as structure disease include HCM and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), and arrhythmogenic abnormalities, which in turn contain long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT). The combination of genetic heart conditions and heavy sport competitions may increase the risk of SCD by stimulation of the malignant ventricular arrhythmias (Corrado, Migliore, et al., 2006). The “mechanical” and “electrical” concepts are two major pathophysiological pathways that contribute to the occurrence of SCD (Thiene, et al., 2010). The sudden and unexpected death resulting from “mechanical” pathway may occur in two conditions: impaired cardiac pump function caused by pulmonary embolism (blockage of the circulation) and as a result of

cardiac tamponade associated with hemopericardium (aortic dissection) (Thiene, et al., 2010). However, “electrical” pathway (arrhythmic) is known as a main factor involved in the occurrence of SCD (Huikuri, et al., 2001). The electrophysiological mechanisms impose their fatal role through the interaction of several variables including an arrhythmogenic substrate (myocardial hypertrophy and inflammation, ventricular aneurysm, and etc.), Regulator (autonomic nervous system, renin-angiotensin system, hydro-electrolyte disturbances, etc.) and trigger factors (extrasystole and sudden increases in heart rate) (Varró and Baczkó, 2010). The arrhythmogenic substrates is not fatal per se; unless the trigger factors act on it in a desirable condition (Ferreira, et al., 2010). The physiological changes during exercise and exhaustive competitions may be a risk factor for malignant ventricular arrhythmias induction; some of these physiological changes are an accumulation of catecholamines, acidosis (drop of pH value), electrolyte imbalance, and deficit of total body water (dehydration) (Heidbuchel and Carré, 2014). It could support the fact that more than 90% of athletes die during exercise training or competition (Bille, et al., 2006, Maron, Thompson, et al., 1996). In other words, the combination of certain heart disease and exhaustive training or onerous competitions is a serious alarm for the SCD (Corrado, et al., 2003). The sympathetic nervous system activity at the highest levels in early-morning hours, exerts a greater pressure on the cardiac muscle and coronary arteries (Myerburg, et al., 1993). Therefore, it is suggested that both athletes and non-athletes should not perform high-intensity exercises in early-morning, particularly people with cardiovascular problems. In addition, heavy sport competitions should preferably be held in other hours.

The causes of SCD in athletes are affected by age. There is a major difference between SCD mechanisms in young athletes (<35 years of age) and older athletes (>35 or 40 years). In young athletes, some of the inherited or congenital cardiac diseases such as cardiomyopathies (HCM, ARVC/D, and dilated cardiomyopathy) and coronary artery anomalies, play a key role in the incidence of SCD, while other inherited cardiac abnormalities like the Marfan syndrome, Long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia, are considered as accessory causes of SCD (Borjesson and Pelliccia, 2009, Talbot, et al., 2002, Ferreira, et al., 2010, Sheppard, 2012). In contrast, the occurrence of SCD in older athletes and in general population is associated with CAD (Corrado, Migliore, et al., 2006). Timely and accurate diagnosis of these abnormalities may be effective in the prevention of sports-related SCD; however, very low rate (about 0.2%) of effective detection has been reported (Moss, 2003, Roberts and Brugada, 2003). Taken together, there are few appropriate suggestions on do's and don'ts of exercise for the athletes with genetic heart problems (Ackerman, et al., 2015, Maron, et al., 2015, Sweeting and Semsarian, 2016): athletes who are diagnosed with structural or arrhythmogenic disorders should not participate in events with high physiological demands such as high-intensity exercise, excessive intensive exercise, and sports competitions. However, there are no impediments to take

advantage of low-intensity exercise (yoga) and gentle sports (golf and bowling). In addition, in the presence of certain arrhythmogenic abnormalities, particularly long QT syndrome, returning to exercise or sport depends on the effectiveness of previous treatment and accurate screening (Ackerman, et al., 2015, Sweeting and Semsarian, 2016). A comprehensive discussion of the pathological mechanisms of SCD is beyond the scope of this chapter. Here we present a brief overview of the most common causes of SCD in young athletes (HCM and ARVC/D) and older athletes (CAD) followed by a brief explanation of the athlete's heart and the effects of ergogenic aids.

HYPERTROPHIC CARDIOMYOPATHY

HCM is an inherited pathological condition in which the myocardium becomes enlarged (more than 1.5 cm), for no good reason (Ramaraj, 2008). HCM is known as the most common type of genetic heart disorder and its incidence rate is approximately 1/200 of the general population (Semsarian, et al., 2015). HCM is considered as a major risk factor for the incidence of SCD, particularly during high-intensity exercises (Corrado, Migliore, et al., 2006). In this context, HCM has played a key role (up to 40% cases) in the incidence of SCD in the US athletes (Maron, Shirani, et al., 1996, Thiene, et al., 2010). Marc-Vivien Foe's sudden death, a 28 year-old veteran midfielder of the Cameroon national soccer team, is one of the most impressive tragedies seen on a soccer; he collapsed in 2003 in the center circle of the soccer field and eventually died after 45 minutes of cardiopulmonary resuscitation (CPR) efforts (Higgins and Andino, 2013). Ventricular fibrillation associated with HCM (found at autopsy) was specified as the cause of his death (Maron, 2005, Higgins and Andino, 2013). HCM is a powerful substrate for arrhythmias induction and finally SCD (Basso, et al., 1999). The various factors such as aortic stenosis, hypertension or high blood pressure, and amyloidosis are associated (trigger factors) with left ventricular hypertrophy (Ramaraj, 2008). Therefore, the absence of these factors must first be confirmed before HCM can be recognized. The obvious morphological changes associated with HCM include left ventricular hypertrophy and myocardial disarray (Östman-Smith, et al., 2008, Borjesson and Pelliccia, 2009). In fact, left ventricular wall becomes thickened asymmetrically (≥ 12 mm), particularly in the anterior septal region (Maron, Shirani, et al., 1996, Shirley and Adirim, 2005). HCM can act as a contributing risk factor for fatal arrhythmias via disorganization of the myocardial cells and fibrosis associated with ischemia (Attari and Dhala, 2004, Maron, 2003). Thickening of the myocardium due to HCM disorder leads to myocardial perfusion defects. In other words, coronary perfusion cannot reach into the thickened regions of the myocardium, and localized ischemia may occur during this situation (Shirley and Adirim, 2005). Coronary perfusion is aggravated during interaction of HCM disease with an increased heart rate, particularly in response to exercise (Shirley

and Adirim, 2005). The clinical symptoms of HCM are chest pain, palpitations, dyspnea, fatigue, pre-syncope, unexplained syncope, and, an abnormal (irregular) electrocardiogram (ECG) pattern, or in some other cases, probably without any sign (Maron, 2002, Östman-Smith, et al., 2008). It should be noted that unexplained syncope during or after exercise training can be a sign of a more serious condition; therefore, athletes should receive a thorough cardiovascular assessment right away after the first attack of syncope (Fuller, 2000, Luckstead, 2002). Left ventricular outflow obstruction may be involved in the onset of syncope through a decrease in cardiac output and cerebral blood flow (Fuller, 2000, Luckstead, 2002). Interestingly, most people (about 90%) involved with HCM disorder have abnormal ECG patterns; some of identified irregular patterns include ST segment depression, T-wave inversion, pathologic Q waves, left atrial enlargement or dilation, conduction delay, and left axis deviation (Drezner, et al., 2013). Multiple mutations (more than 150) in various genes are involved in the etiology of this disease (Corrado, et al., 1998, Shirley and Adirim, 2005). Among the 10 identified genes associated with HCM, three of them play a crucial role: cardiac troponin T on chromosome 1, β -myosin heavy chain on chromosome 14, and myosin-binding protein C on chromosome 11 (Fuller, 2000, Shirley and Adirim, 2005). As already explained, HCM is the main cause of SCD among young athletes (Sheppard, 2012). It leaves its lethal role through ventricular tachycardia/fibrillation (VT/F) (Borjesson and Pelliccia, 2009). In fact, VT/F may be considered as the first clinical manifestation of HCM which usually offers itself in the context of exercise training and sport competitions (Borjesson and Pelliccia, 2009). One of the most reliable tools available for diagnosis of HCM is two-dimensional echocardiography. This device can detect non-dilated left ventricular hypertrophy in the presence of different cardiac disorders and systemic disease which may produce a similar hypertrophy (Pfister, et al., 2000, Corrado, et al., 1998). Thus stated, excessive intensive training combined with heavy competitions may increase the risk of SCD in the context of cardiac disorders via potentiation of the present disease or arrhythmias induction. For example, the frequent occurrence of acute myocardial ischemia during high-intensity exercise in HCM patients may stimulate cell death in myocardial and eventually create a myocardial replacement fibrosis; which in turn augments electrical instability of the ventricles (Maron, et al., 2004). Therefore, athletes with HCM clinical diagnosis or those who are suspected of having HCM disease should be excluded from the high-intensity exercise training or events with high physiological demands. This recommendation is independent of variables such as age, gender, and phenotypic appearance. In addition, it does not change its policy through the presence or absence of symptoms, left ventricular outflow obstruction, and previous treatments (Maron, et al., 2005).

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/DYSPLASIA

ARVC/D is another important inherited cause of SCD among young athletes (Corrado, et al., 1990, Thiene, et al., 2010). The main morphological characteristic of ARVC/D is the replacement of fibrous-fatty plaques (fibrous and/or adipose tissue) with the dead right ventricle myocyte. Right ventricle myocardium is the main target of this disorder. However, left ventricular involvement is also observed in up to 50% of cases. Ventricle myocyte loss and distribution of fibrous-fatty plaques on the epicardial surface may increase the risk of SCD through ventricular and supraventricular arrhythmias induction (Thiene, et al., 2007, Calkins, 2013, Shirley and Adirim, 2005, Sheppard, 2012). As recorded in the Veneto region of Italy, ARVC/D is the first leading cause of SCD in the young athletes and second leading cause of SCD among young non-athletes (Corrado, et al., 1990, Basso, et al., 2001, Thiene, et al., 2010). However, as previously reported, HCM is known as the most common cause of SCD in the US young athletes (Maron, Shirani, et al., 1996, Thiene, et al., 2010). There might be a connection between ARVC/D disorder and SCD of US athletes since the lethal effect of ARVC/D is less than 5% (Maron, et al., 2006, Maron, 2007). There is no detailed explanation for the differences in the causes of SCD among Italian and US athletes; however, the relatively frequent incidence of ARVC/D in the Italian athletes may be justified by the presence of a unique genetic context in this population (Thiene, et al., 1988, Maron, 2007). Competitive sports are considered as a serious threat for ARVC/D patients, so that the risk of SCD during heavy competition for such patients is 5.4 times higher than routine activities (Corrado, et al., 2003, Borjesson and Pelliccia, 2009). Different mechanisms are involved in the etiology of arrhythmias. For example, stretching force enhancement on the abnormal or diseased myocardium due to frequent increased pressure overload during exercise may result in ventricular arrhythmia and/or potentiate the mechanisms responsible for re-entrant arrhythmias. In addition, “supersensitivity” to catecholamines following impairment of sympathetic nerve trunks by distribution of fibrous-fatty plaques on the epicardial surface may contribute to ventricular arrhythmias induction (Marcus, et al., 2010, Wichter, et al., 1994, Borjesson and Pelliccia, 2009). Some clinical diagnostic criteria for ARVC/D include abnormalities and irregularities (depolarization and repolarization) of right ventricular chamber (Calkins, 2013, Sweeting and Semsarian, 2016). Thorough and regular cardiovascular assessments will help to identify latent and dangerous disorders that can have irremediable consequences. Therefore, we strongly recommend that regular assessment of athlete’s cardiovascular system be performed by a cardiologist. ECG and echocardiography are not ideal diagnostic tools for ARVC/D disorder because the capabilities of such devices are limited to distinguishing ARVC/D from benign physiological changes in the myocardium. Nevertheless, magnetic resonance

imaging may have appropriate sensitivity and specificity for the diagnosis of ARVC/D disorder (Maron, Gardin, et al., 1995, Shirley and Adirim, 2005). Finally, like athletes with HCM, athletes with ARVC/D should also be excluded from the high-intensity exercise training or events with high physiological demands (Maron, et al., 2005).

CORONARY ARTERY DISEASE

Occlusion or blockage (>75%) of the main coronary arteries (commonly the proximal left anterior descending [LAD] coronary artery) is the most common cause of SCD in the older athletes (more than 35 years) (Tabib, et al., 1999, Mohlenkamp, et al., 2008, Sheppard, 2012). However, this disorder plays a minor (2% to 3%) role in the SCD of young athletes (Maron, et al., 2009, Corrado, Basso, et al., 2006). Even the presence of a single obstructive plaque within the LAD may be sufficient for ventricular fibrillation induction and SCD (Corrado, et al., 1994, Thiene, et al., 2010). Interestingly, patients with CAD may experience a transient contractile dysfunction in the left ventricle due to the post-exercise stunning (Koenig and Ernst, 2000). Coronary atheroma, as the cause of SCD, is not associated with various factors such as rupture of the plaque, fibrosis, thrombosis, and acute infarction (Koenig and Ernst, 2000). Clearly enough, adverse cardiac effects of exercise may be increased along with the following conditions in both women and men: obesity, lipid disorders, diabetes, hypertension, and family history of cardiovascular abnormalities (Koenig and Ernst, 2000, Sheppard, 2012). A single bout of exercise may increase the relative risk of acute coronary syndromes (ACS) and thrombosis during or immediately after workout; however, the absolute risk associated with exercise for such patients is approximately low. This adverse event may be due to the inductive effects of exercise on atherosclerotic plaque rupture and activation of blood coagulation system (Kumar, et al., 2011). SCD is primarily associated with familial hypercholesterolemia. Symptoms of this disorder are rare, and SCD has frequently been initially observed in the affected patients (Chandra, et al., 2013). It should be noted that young age does not appear to interfere with coronary atheroma as an incidence mechanism of SCD. Within this framework, widespread diffuse atheroma had been observed within all coronary arteries of a young (an 11-year-old girl) victim of SCD. She had been completely asymptomatic prior to the incident, and collapsed and died during a cross-country running; noting the fact that she had a strong family history of high cholesterol (Sheppard, 2012). However, pathologists and cardiologists should be conservative in attributing SCD to CAD, unless in the presence of a remarkable atheroma plaque within the left main stem (LMC) coronary artery, LAD or right coronary (RCA) artery (Sheppard, 2012).

ATHLETE'S HEART

Various hemodynamic and electrophysiological factors respond significantly to exercise in a healthy heart. Some of the physiological changes in response to acute high-intensity aerobic exercise include substantial increases in skeletal muscle oxygen consumption and cardiac output. These changes, along with other physiological responses create several cardiovascular adaptations in long term or in response to chronic exercise (Futtermann and Myerburg, 1998, Koester, 2001). In fact, chronic exercise produces certain morphological changes in the heart (cardiac dimensional alterations), which eventually may manifest as functional changes. These adaptations are changes within the left ventricle (increase of the cavity size and thickening of the wall) and left atrial (increase of the size) (Maron Barry and Pelliccia, 2006, Pelliccia, et al., 1999, Pelliccia, Maron, et al., 2005). Physiological cardiac hypertrophy or well-trained athlete hypertrophy was first introduced in 1935 (Wight and Salem, 1995). The amount and shape of adaptations are influenced by age, gender, ethnicity, and different training variables such as intensity; and the achieved changes can be evaluated by ECG and echocardiography (Maron, 2005, Koester, 2001, Sharma, 2003). Left ventricle hypertrophy caused by exercise training is usually symmetric, and the achieved changes are influenced by "Use it or Lose it principle" of fitness (i.e., the rapid disappearance of adaptations due to cessation of exercise) (Futtermann and Myerburg, 1998, Koester, 2001). Taken together, mild structural and morphological alterations in the heart caused by exercise training are called Athlete's Heart, which in turn improves heart function (cardiac output) through increasing the rate of left ventricular filling during the diastolic period and amplification of stroke volume (Chandra, et al., 2013, Maron, Pelliccia, et al., 1995, Shirley and Adirim, 2005). However, in some cases, the achieved adaptations or left ventricular hypertrophy are so considerable that distinguishing physiological hypertrophy from the most common pathological forms such as HCM turns into a great challenge (Maron, Pelliccia, et al., 1995, Shirley and Adirim, 2005). By the same token, in a few HCM patients, ventricular hypertrophy is almost close to physiological form (i.e., relatively mild hypertrophy) (Maron, Pelliccia, et al., 1995, Shirley and Adirim, 2005). Altogether, pathological aspects of heart remodeling associated with excessive endurance training may be higher than its adaptive effects (Maron, Pelliccia, et al., 1995, Patil, et al., 2012). Distinguishing physiological adaptations from pathological conditions is of high importance because a false diagnosis may bring about an SCD in athletes (Chandra, et al., 2013). Awareness of the certain differences between HCM and athlete's heart is truly helpful for the diagnosis process. Some of these differences include (Maron, Pelliccia, et al., 1995, Koester, 2001): left ventricular hypertrophy of HCM patients is substantially unbalanced or asymmetric. In contrast, differences in the thickness of various segments of the ventricular wall (about 1 to 2 mm) are not much impressive in the athlete's heart. One of the main features of athlete's heart is the enlarged (>55 mm) left ventricular end-

diastolic dimension. Ventricular cavity size of HCM patients is often small, except in case of heart failures (i.e., end-stage of HCM). The patterns of left ventricular filling may be irregular in patients with HCM. Yet, filling patterns associated with athlete's heart are normal. Finally, in agreement with Use it or Lose it principle, 3 months of detraining (deconditioning or minimal exercise) results in the relative recovery of the athlete's heart (2 to 5 mm reduction in left ventricular hypertrophy). However, in HCM patients, left ventricular hypertrophy remained unchanged over this time period.

ERGOGENIC AIDS OR PERFORMANCE-ENHANCING SUBSTANCES

The use of ergogenic aids (drugs or other substances) for the enhancement of athletic performance is considered as doping (Baron, et al., 2007). The use of ergogenic aids takes place usually in all sports at various levels of competition by athletes of different age (Fernandez and Hosey, 2009). Doping may be applied for multiple reasons such as increasing athletic performance and overcoming various stresses associated with competition days (Reardon and Creado, 2014). A large proportion of unexplained etiology of SCD in young athletes could be attributed to the use of ergogenic aids (Puranik, et al., 2005, Borjesson and Pelliccia, 2009). Lethal ventricular tachyarrhythmias, as one of the main causes of athletes SCD, may be sensitive to ergogenic aids (Estes, et al., 2005, Borjesson and Pelliccia, 2009). Some of the ergogenic substrates are anabolic steroids, erythropoietin (non-steroidal), ephedrine (stimulant), and growth hormone (Estes, et al., 2005, Chandra, et al., 2013). Frequent intake of androgenic-anabolic steroid is considered as a major risk factor for producing various pathological conditions such as lipid metabolism disorders, hypertension, cardiac hypertrophy, premature atherosclerosis, acute myocardial infarction, and SCD (Melchert and Welder, 1995, Dhar, et al., 2005). In addition, cardiomyopathy may be achieved in response to certain agents like ephedrine and anabolic-androgenic steroid (Dhar, et al., 2005). Cardiovascular complications associated with the anabolic-androgenic steroids intake may mediate via hypothetical mechanisms which are atherogenic, thrombosis, and vasospasm (Melchert and Welder, 1995, Borjesson and Pelliccia, 2009). Cocaine intake can lead to serious pathological responses such as local ischemia (oral abuse) and fatal arrhythmias (inhalant abuse). Local ischemia and infarction associated with cocaine abuse may be achieved by vasospasm (Reisdorff and Proding, 1998, Koester, 2001). Something about 3.1% of SCD are attributed to cocaine abuse. This agent may impose its lethal effects through the generation of small vessel abnormalities, left ventricular hypertrophy, and premature coronary-artery atherosclerosis disease (Lucena, et al., 2010). Altogether, ergogenic aids or certain prohibited substances (peptide hormones, anabolic steroids, and stimulants) may contribute to the induction of various ventricular arrhythmias (Furlanello, et al., 2003). Adverse cardiovascular effects of ergogenic aids

might be higher in extreme and stressful situations such as physical exhaustion (Estes, et al., 2005); circumstances like sport competitions. Consequently, the possibility of prohibited ergogenic aids abuse as the cause of lethal arrhythmias must be taken into consideration, particularly in the absence of symptoms of heart disorders (Furlanello, et al., 2003). In addition, toxicological screening should be performed after all cases of SCD in athletes to confirm or reject the hypothesis of the ergogenic aids as a cause of SCD (Dhar, et al., 2005, Borjesson and Pelliccia, 2009).

SCREENING CHALLENGES

The causes of SCD are often clinically silent or indicate only non-specific signs before the incidence of events (Shirley and Adirim, 2005). Accurate and timely diagnosis of latent cardiovascular disorders could significantly reduce SCD in general population and athletes (Corrado, et al., 2005). According to Italian experience, pre-participation cardiovascular screening is effective in preventing the occurrence of SCD in young athletes with the HCM disorder (Corrado, et al., 1998, Corrado, et al., 2005). Screening plays a special role in the survival and this has been confirmed by the Veneto Region of Italy (Corrado, et al., 1998). The content of available screening strategies usually covers items such as personal and family history, check-up or physical examination, and expert evaluation of the cardiovascular system by ECG and echocardiography (Fuller, 2000, Shirley and Adirim, 2005). American Heart Association (AHA) and European Society of Cardiology (ESC) have presented certain pre-participation cardiovascular screenings. The US approach recommends a 12-point protocol for screening, which its composition are family history, physical examination, and symptoms. Interestingly, the main focus of this protocol is the family history items and only four its points are associated with the physical examination component (Chandra, et al., 2010, Chandra, et al., 2013, Crawford, 2007). However, in the Italian screening model, along with family history, physical examination, and symptoms; 12-lead ECG test is also presented (Ljungqvist, et al., 2009). The ECG-inclusive screening protocol has been also proposed by the ESC (Corrado, et al., 2010). The ECG is considered as gold-standard test for diagnosis of a wide range of cardiac disorders such as those which are associated with electrical abnormalities and ion channelopathies (Maron, 2002, Marcus, 2000). Therefore, using the ECG in the screening protocol amplifies diagnostic aspects of SCD risk factors (Chandra, et al., 2013). Several abnormalities such as HCM and ARVC/D, are also identified through the ECG test (>90% HCM patients and >75% ARVC/D patients) (Maron, 2002, Marcus, 2000). In contrast, the specificity of the ECG test for the screening of athletes is relatively low because of the limitations of this tool in the diagnosis of physiological changes (athlete's heart) from pathological conditions (Shirley and Adirim, 2005). For this major limitation, AHA does not recommend regular use of this tool for screening athletes (Chandra, et al.,

2010). Echocardiography is the appropriate test for assessment of structural and functional heart disorders and prevents the additional costs associated with inevitable follow-up because of false-positive results in the athletes (Maron, 1997). However, there are certain limitations associated with echocardiography such as its failure in the diagnosis of left ventricular hypertrophy until the age of adolescence or even further (Maron, 1997). The echocardiography is more accurate compared with the ECG test for the diagnosis of conditions like left ventricular hypertrophy; however, it costs more than the latter (around \$400 to \$1600) (Devereux, et al., 1987, Maron, 1997). In terms of cost-effectiveness of the screening protocols, it has been reported that Italian screening model is more appropriate than US model (Wheeler, et al., 2010). As a final note, automated external defibrillators should be present in all exercise environments as an important part of the comprehensive emergency action plan for sudden cardiac arrest (Rothmier and Drezner, 2009). Improvement of survival is influenced by rapid diagnosis of cardiac arrest, presence of an expert CPR team, and uninterrupted access to automated external defibrillators (Chandra, et al., 2013). Rapid defibrillation over a cardiac arrest is crucial. Collapse of an athlete should be considered (speculation) as a cardiac arrest and an immediate application of automated external defibrillator is highly recommended (Rothmier and Drezner, 2009). Timely defibrillation plays a vital role in the survival of cardiac arrest victims and may reverse the SCD in the athletes (Drezner and Rogers, 2006, Rothmier and Drezner, 2009).

SUMMARY

There is a common contention among most people throughout the world that athletes are the outstanding symbols of health and strength. Though it is firmly documented that exercise can increase longevity by reducing the mortality risk factors (Reimers, et al., 2012, Gremeaux, et al., 2012). The tragic incidence of SCD in young athletes nullifies this fact and generates widespread public and media attention accordingly. The SCD in athletes as a major global health problem requires scholarly attention and scientific scrutiny. Its incidence rate is higher for athletes in comparison with non-athlete counterparts. The general belief that doping is a main cause of SCD in athletes is contradicted by the numerous SCD events which were brought about by latent underlying cardiovascular disorders. However, the role of doping remains as a possible cause of unexplained etiology of SCD in athletes. Male athletes are more hit as SCD victims than females. The main causes of SCD vary in respect to young (HCM and ARVC/D) and older (CAD) athletes. Yet, the role of excessive intensive training and chronic exposure to very long distance races (marathons, ultra-marathons, Ironman distance triathlons, and 100-mile bicycle) should not be overlooked as a cardiovascular risk factor (Patil, et al., 2012). On the other hand, it is unfavorable to neglect comprehensive physiological

adaptations due to safe exercise programs. According to Gene Tunney (US professional boxer), "exercise should be regarded as a tribute to the heart."

Accurate and systematic screening of athletes is critical to prevent the incidence of SCD. The ECG-inclusive screening protocols are found appropriate. Echocardiography is recommended for the diagnosis of heart physiological adaptations from the pathological conditions. The 2-dimensional echocardiography is considered as an ideal tool for the diagnosis of HCM disorder. The presence of automated external defibrillators and an expert CPR team are truly effective for the improvement of survival in athletes suffering cardiac arrest. At the end, we hope that no athlete ever experiences such a tragic incident throughout his/her life. We also hope that the merits of exercising help everyone live a healthy life.

REFERENCES

- Ackerman, Michael J, Douglas P Zipes, Richard J Kovacs, and Barry J Maron. 2015. "Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities: Task Force 10: The Cardiac Channelopathies." *Circulation* 132: e326-e29.
- Amital, Howard, Michael Glikson, Moshe Burstein, Arnon Afek, Ronit Sinnreich, Yuval Weiss, and Vered Israeli. 2004. "Clinical Characteristics of Unexpected Death among Young Enlisted Military Personnel: Results of a Three-Decade Retrospective Surveillance." *CHEST Journal* 126: 528-33.
- Amsterdam, Ezra A. 1990. "Sudden Death During Exercise." *Cardiology* 77: 411-17.
- Aschar-Sobbi, Roozbeh, Farzad Izaddoustdar, Adam S Korogyi, Qionglng Wang, Gerrie P Farman, FengHua Yang, Wallace Yang, David Dorian, Jeremy A Simpson, and Jari M Tuomi. 2015. "Increased Atrial Arrhythmia Susceptibility Induced by Intense Endurance Exercise in Mice Requires Tnfa." *Nature communications* 6.
- Attari, Mehran, and Anwer Dhala. 2004. "Role of Invasive and Noninvasive Testing in Risk Stratification of Sudden Cardiac Death in Children and Young Adults: An Electrophysiologic Perspective." *Pediatric Clinics* 51: 1355-78.
- Baron, David A, David M Martin, and Samir Abol Magd. 2007. "Doping in Sports and Its Spread to at-Risk Populations: An International Review." *World Psychiatry* 6: 54-59.
- Basso, C, G Thiene, D Corrado, G Buja, P Melacini, and A Nava. "Hypertrophic Cardiomyopathy: Pathologic Evidence of Ischemic Damage in Young Sudden Death Victims." Paper presented at the LABORATORY INVESTIGATION, 1999.
- Basso, Cristina, Fiorella Calabrese, Domenico Corrado, and Gaetano Thiene. 2001. "Postmortem Diagnosis in Sudden Cardiac Death Victims: Macroscopic, Microscopic and Molecular Findings." *Cardiovascular research* 50: 290-300.

- Bille, Karin, David Figueiras, Patrick Schamasch, Lukas Kappenberger, Joel I Brenner, Folkert J Meijboom, and Erik J Meijboom. 2006. "Sudden Cardiac Death in Athletes: The Lausanne Recommendations." *European Journal of Cardiovascular Prevention & Rehabilitation* 13: 859-75.
- Borjesson, M, and A Pelliccia. 2009. "Incidence and Aetiology of Sudden Cardiac Death in Young Athletes: An International Perspective." *British journal of sports medicine* 43: 644-48.
- Calkins, H. 2013. "Arrhythmogenic Right Ventricular Dysplasia." *Curr Probl Cardiol* 38: 103-23.
- Chandra, Navin, Rachel Bastiaenen, Michael Papadakis, and Sanjay Sharma. 2013. "Sudden Cardiac Death in Young Athletes: Practical Challenges and Diagnostic Dilemmas." *Journal of the American College of Cardiology* 61: 1027-40.
- Chandra, Navin, Michael Papadakis, and Sanjay Sharma. 2010. "Preparticipation Screening of Young Competitive Athletes for Cardiovascular Disorders." *The Physician and sportsmedicine* 38: 54-63.
- Corrado, Domenico, Cristina Basso, Andrea Pavei, Pierantonio Michieli, Maurizio Schiavon, and Gaetano Thiene. 2006. "Trends in Sudden Cardiovascular Death in Young Competitive Athletes after Implementation of a Preparticipation Screening Program." *Jama* 296: 1593-601.
- Corrado, Domenico, Cristina Basso, Alessandro Poletti, Annalisa Angelini, Marialuisa Valente, and Gaetano Thiene. 1994. "Sudden Death in the Young. Is Acute Coronary Thrombosis the Major Precipitating Factor?". *Circulation* 90: 2315-23.
- Corrado, Domenico, Cristina Basso, Giulio Rizzoli, Maurizio Schiavon, and Gaetano Thiene. 2003. "Does Sports Activity Enhance the Risk of Sudden Death in Adolescents and Young Adults?". *Journal of the American College of Cardiology* 42: 1959-63.
- Corrado, Domenico, Cristina Basso, Maurizio Schiavon, and Gaetano Thiene. 1998. "Screening for Hypertrophic Cardiomyopathy in Young Athletes." *New England Journal of Medicine* 339: 364-69.
- Corrado, Domenico, Federico Migliore, Cristina Basso, and Gaetano Thiene. 2006. "Exercise and the Risk of Sudden Cardiac Death." *Herz Kardiovaskuläre Erkrankungen* 31: 553-58.
- Corrado, Domenico, Antonio Pelliccia, Hans Halvor Bjørnstad, Luc Vanhees, Alessandro Biffi, Mats Borjesson, Nicole Panhuyzen-Goedkoop, Asterios Deligiannis, Erik Solberg, and Dorian Dugmore. 2005. "Cardiovascular Pre-Participation Screening of Young Competitive Athletes for Prevention of Sudden Death: Proposal for a Common European Protocol." *European heart journal* 26: 516-24.
- Corrado, Domenico, Antonio Pelliccia, Hein Heidbuchel, Sanjay Sharma, Mark Link, Cristina Basso, Alessandro Biffi, Gianfranco Buja, Pietro Delise, and Ihor Gussac.

2010. "Recommendations for Interpretation of 12-Lead Electrocardiogram in the Athlete." *European heart journal* 31: 243-59.
- Corrado, Domenico, Gaetano Thiene, Andrea Nava, Lino Rossi, and Natale Pennelli. 1990. "Sudden Death in Young Competitive Athletes: Clinicopathologic Correlations in 22 Cases." *The American journal of medicine* 89: 588-96.
- Crawford, Michael H. 2007. "Screening Athletes for Heart Disease." *Heart* 93: 875-79.
- De Backer, Guy, Ettore Ambrosionie, Knut Borch-Johnsen, Carlos Brotons, Renata Cifkova, Jean Dallongeville, Shah Ebrahim, Ole Faergeman, Ian Graham, and Giuseppe Mancia. 2003. "European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of Eight Societies and by Invited Experts)." *European Journal of Cardiovascular Prevention & Rehabilitation* 10: S1-S78.
- Devereux, RICHARD B, PAUL N Casale, DONALD C Wallerson, PAUL Kligfield, Isaac W Hammond, PHILIP R Liebson, Emilio Campo, Daniel R Alonso, and JOHN H Laragh. 1987. "Cost-Effectiveness of Echocardiography and Electrocardiography for Detection of Left Ventricular Hypertrophy in Patients with Systemic Hypertension." *Hypertension* 9: II69.
- Dhar, Ritesh, C William Stout, Mark S Link, Munther K Homoud, Jonathan Weinstock, and NA Mark Estes. "Cardiovascular Toxicities of Performance-Enhancing Substances in Sports." Paper presented at the Mayo Clinic Proceedings, 2005.
- Drezner, Jonathan A, Euan Ashley, Aaron L Baggish, Mats Börjesson, Domenico Corrado, David S Owens, Akash Patel, Antonio Pelliccia, Victoria L Vetter, and Michael J Ackerman. 2013. "Abnormal Electrocardiographic Findings in Athletes: Recognising Changes Suggestive of Cardiomyopathy." *British Journal of Sports Medicine* 47: 137-52.
- Drezner, Jonathan A, and Kenneth J Rogers. 2006. "Sudden Cardiac Arrest in Intercollegiate Athletes: Detailed Analysis and Outcomes of Resuscitation in Nine Cases." *Heart Rhythm* 3: 755-59.
- Estes, NA Mark, Robert Kloner, Brian Olshansky, and Renu Virmani. 2005. "Task Force 9: Drugs and Performance-Enhancing Substances." *Journal of the American College of Cardiology* 45: 1368-69.
- Fazelifar, Amir Farjam, Peyman Ashrafi, Majid Haghjoo, Zahra Ojaghi Haghighi, Hooman Bakhshandeh Abkenar, Ashrafossadat Ashour, Shahrbanou Azari, Azam Forghanian, and Mohammad Ali Sadr-Ameli. 2009. "Predictors of Ventricular Tachycardia Induction in Syncopal Patients with Mild to Moderate Left Ventricular Dysfunction." *Cardiol J* 16: 327-31.
- Fernandez, Marifel Mitzi F, and Robert G Hosey. 2009. "Performance-Enhancing Drugs Snare Nonathletes, Too: High School Athletes Aren't the Only Ones Seeking an

- Edge. Here Are the Red Flags and Unexpected Drugs to Watch For.” *Journal of Family Practice* 58: 16-24.
- Ferreira, Marcelo, Paulo Roberto Santos-Silva, Luiz Carlos de Abreu, Vitor E Valenti, Vanessa Crispim, Caio Imaizumi, Celso Ferreira Filho, Neif Murad, Adriano Meneghini, and Andrés R Pérez Riera. 2010. “Sudden Cardiac Death Athletes: A Systematic Review.” *BMC Sports Science, Medicine and Rehabilitation* 2: 19.
- Fuchs, Flávio D. “Why Do Black Americans Have Higher Prevalence of Hypertension?”: Am Heart Assoc, 2011.
- Fuller, Colin M. 2000. “Cost Effectiveness Analysis of Screening of High School Athletes for Risk of Sudden Cardiac Death.” *Medicine and Science in Sports and Exercise* 32: 887-90.
- Furlanello, Francesco, Stefano Bentivegna, Riccardo Cappato, and Luigi De Ambroggi. 2003. “Arrhythmogenic Effects of Illicit Drugs in Athletes.” *Italian heart journal: official journal of the Italian Federation of Cardiology* 4: 829-37.
- Futerman, Laurie G, and Robert Myerburg. 1998. “Sudden Death in Athletes.” *Sports Medicine* 26: 335-50.
- Garcia, Julia Helena, and Mildred Patrícia Ferreira da Costa. 2011. “Sudden Cardiac Death in Athletes: Protocols and Routines of Professional Soccer Clubs in São Paulo.” *Revista Brasileira de Medicina do Esporte* 17: 161-65.
- Greameaux, Vincent, Mathieu Gayda, Romuald Lepers, Philippe Sosner, Martin Juneau, and Anil Nigam. 2012. “Exercise and Longevity.” *Maturitas* 73: 312-17.
- Harmon, Kimberly G, Jonathan A Drezner, Mathew G Wilson, and Sanjay Sharma. 2014. “Incidence of Sudden Cardiac Death in Athletes: A State-of-the-Art Review.” *Heart* 100: 1227-34.
- Heidbuchel, Hein, and Francois Carré. 2014. “Exercise and Competitive Sports in Patients with an Implantable Cardioverter-Defibrillator.” *European heart journal* 35: 3097-102.
- Higgins, John P, and Aldo Andino. 2013. “Soccer and Sudden Cardiac Death in Young Competitive Athletes: A Review.” *Journal of sports medicine* 2013.
- Holst, Anders Gaarsdal, Bo Gregers Winkel, Juliane Theilade, Ingrid Bayer Kristensen, Jørgen Lange Thomsen, Gyda Lolk Ottesen, Jesper Hastrup Svendsen, Stig Haunsø, Eva Prescott, and Jacob Tfelt-Hansen. 2010. “Incidence and Etiology of Sports-Related Sudden Cardiac Death in Denmark—Implications for Preparticipation Screening.” *Heart Rhythm* 7: 1365-71.
- Huikuri, Heikki V, Agustin Castellanos, and Robert J Myerburg. 2001. “Sudden Death Due to Cardiac Arrhythmias.” *New England Journal of Medicine* 345: 1473-82.
- Koenig, Wolfgang, and Edzard Ernst. 2000. “Exercise and Thrombosis.” *Coronary artery disease* 11: 123-27.

- Koester, Michael C. 2001. "A Review of Sudden Cardiac Death in Young Athletes and Strategies for Preparticipation Cardiovascular Screening." *Journal of athletic training* 36: 197.
- Kumar, Arun, Subrata Kar, and William P Fay. 2011. "Thrombosis, Physical Activity, and Acute Coronary Syndromes." *Journal of applied physiology* 111: 599-605.
- Ljungqvist, Arne, Peter Jenoure, Lars Engebretsen, Juan Manuel Alonso, Roald Bahr, Anthony Clough, Guido De Bondt, Jiri Dvorak, Robert Maloley, and Gordon Matheson. 2009. "The International Olympic Committee (Ioc) Consensus Statement on Periodic Health Evaluation of Elite Athletes March 2009." *British journal of sports medicine* 43: 631-43.
- Lucena, Joaquin, Mario Blanco, Carmen Jurado, Antonio Rico, Manuel Salguero, Rafael Vazquez, Gaetano Thiene, and Cristina Basso. 2010. "Cocaine-Related Sudden Death: A Prospective Investigation in South-West Spain." *European Heart Journal: ehj* 557.
- Luckstead, Eugene F. 2002. "Cardiac Risk Factors and Participation Guidelines for Youth Sports." *Pediatric Clinics of North America* 49: 681-707.
- Marcus, Frank I. 2000. "Electrocardiographic Features of Inherited Diseases That Predispose to the Development of Cardiac Arrhythmias, Long Qt Syndrome, Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia, and Brugada Syndrome." *Journal of electrocardiology* 33: 1-10.
- Marcus, Frank I, William J McKenna, Duane Sherrill, Cristina Basso, Barbara Bauce, David A Bluemke, Hugh Calkins, Domenico Corrado, Moniek GPJ Cox, and James P Daubert. 2010. "Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia." *European heart journal: ehj* 025.
- Maron, Barry J. "How Should We Screen Competitive Athletes for Cardiovascular Disease?": Eur Soc Cardiology, 2005.
- Maron, Barry J. 2007. "Hypertrophic Cardiomyopathy and Other Causes of Sudden Cardiac Death in Young Competitive Athletes, with Considerations for Preparticipation Screening and Criteria for Disqualification." *Cardiology clinics* 25: 399-414.
- Maron, Barry J. 2002. "Hypertrophic Cardiomyopathy: A Systematic Review." *Jama* 287: 1308-20.
- Maron, Barry J. 1997. "Risk Profiles and Cardiovascular Preparticipation Screening of Competitive Athletes." *Cardiology clinics* 15: 473-83.
- Maron, Barry J. 2003. "Sudden Death in Young Athletes." *New England Journal of Medicine* 349: 1064-75.
- Maron, Barry J, Michael J Ackerman, Rick A Nishimura, Reed E Pyeritz, Jeffrey A Towbin, and James E Udelson. 2005. "Task Force 4: Hcm and Other Cardiomyopathies, Mitral Valve Prolapse, Myocarditis, and Marfan Syndrome." *Journal of the American College of Cardiology* 45: 1340-45.

- Maron, Barry J, Bernard R Chaitman, Michael J Ackerman, Antonio Bayés De Luna, Domenico Corrado, Jane E Crosson, Barbara J Deal, David J Driscoll, NA Mark Estes, and Claudio Gil S Araújo. 2004. "Recommendations for Physical Activity and Recreational Sports Participation for Young Patients with Genetic Cardiovascular Diseases." *Circulation* 109: 2807-16.
- Maron, Barry J, Joseph J Doerer, Tammy S Haas, David M Tierney, and Frederick O Mueller. 2006. "Profile and Frequency of Sudden Deaths in 1,463 Young Competitive Athletes: From a 25-Year Us National Registry, 1980–2005." *Circulation* 114: II_830-II_30.
- Maron, Barry J, Joseph J Doerer, Tammy S Haas, David M Tierney, and Frederick O Mueller. 2009. "Sudden Deaths in Young Competitive Athletes." *Circulation* 119: 1085-92.
- Maron, Barry J, Julius M Gardin, John M Flack, Samuel S Gidding, Tom T Kurosaki, and Diane E Bild. 1995. "Prevalence of Hypertrophic Cardiomyopathy in a General Population of Young Adults." *Circulation* 92: 785-89.
- Maron, Barry J, Tammy S Haas, Caleb J Murphy, Aneesha Ahluwalia, and Stephanie Rutten-Ramos. 2014. "Incidence and Causes of Sudden Death in Us College Athletes." *Journal of the American College of Cardiology* 63: 1636-43.
- Maron Barry, J, and A Pelliccia. 2006. "The Heart of Trained Athletes Cardiac Remodeling and the Risks of Sports, Including Sudden Death Circulation." *NEJM* 114: 1633-44.
- Maron, Barry J, Antonio Pelliccia, and Paolo Spirito. 1995. "Cardiac Disease in Young Trained Athletes." *Circulation* 91: 1596-601.
- Maron, Barry J, William C Roberts, and STEPHEN E Epstein. 1982. "Sudden Death in Hypertrophic Cardiomyopathy: A Profile of 78 Patients." *Circulation* 65: 1388-94.
- Maron, Barry J, William C Roberts, Hugh A Mcallister, Douglas R Rosing, and Stephen E Epstein. 1980. "Sudden Death in Young Athletes." *Circulation* 62: 218-29.
- Maron, Barry J, Jamshid Shirani, Liviu C Poliac, Robert Mathenge, William C Roberts, and Frederick O Mueller. 1996. "Sudden Death in Young Competitive Athletes: Clinical, Demographic, and Pathological Profiles." *Jama* 276: 199-204.
- Maron, Barry J, Paul D Thompson, James C Puffer, Christopher A McGrew, William B Strong, Pamela S Douglas, Luther T Clark, Matthew J Mitten, Michael H Crawford, and Dianne L Atkins. 1996. "Cardiovascular Preparticipation Screening of Competitive Athletes." *Circulation* 94: 850-56.
- Maron, Barry J, James E Udelson, Robert O Bonow, Rick A Nishimura, Michael J Ackerman, NA Mark Estes, Leslie T Cooper, Mark S Link, and Martin S Maron. 2015. "Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis." *Circulation* 132: e273-e80.

- Maron, Barry Joel. *The Athlete's Heart and Cardiovascular Disease*. WB Saunders, 1997.
- Maron, BJ. 2005. "Distinguishing Hypertrophic Cardiomyopathy from Athlete's Heart: A Clinical Problem of Increasing Magnitude and Significance." *HEART-LONDON-BMJ PUBLISHING GROUP* 91: 1380.
- McCaffrey, F. M., D. S. Braden, and W. B. Strong. 1991. "Sudden Cardiac Death in Young Athletes. A Review." *Am J Dis Child* 145: 177-83.
- Melchert, Russell B, and Allison A Welder. 1995. "Cardiovascular Effects of Androgenic-Anabolic Steroids." *Medicine and Science in Sports and Exercise* 27: 1252-62.
- Miura, K, H Nakagawa, Y Morikawa, S Sasayama, A Matsumori, K Hasegawa, Y Ohno, A Tamakoshi, T Kawamura, and Y Inaba. 2002. "Epidemiology of Idiopathic Cardiomyopathy in Japan: Results from a Nationwide Survey." *Heart* 87: 126-30.
- Mohlenkamp, S., N. Lehmann, F. Breuckmann, M. Brocker-Preuss, K. Nassenstein, M. Halle, T. Budde, K. Mann, J. Barkhausen, G. Heusch, K. H. Jockel, and R. Erbel. 2008. "Running: The Risk of Coronary Events: Prevalence and Prognostic Relevance of Coronary Atherosclerosis in Marathon Runners." *Eur Heart J* 29: 1903-10.
- Moss, Arthur J. 2003. "Long Qt Syndrome." *Jama* 289: 2041-44.
- Myerburg, Robert J, Kenneth M Kessler, and Agustin Castellanos. 1993. "Sudden Cardiac Death: Epidemiology, Transient Risk, and Intervention Assessment." *Annals of internal medicine* 119: 1187-97.
- O'Keefe, James H, Robert Vogel, Carl J Lavie, and Loren Cordain. 2011. "Exercise Like a Hunter-Gatherer: A Prescription for Organic Physical Fitness." *Progress in cardiovascular diseases* 53: 471-79.
- Östman-Smith, Ingegerd, Göran Wettrell, Barry Keeton, Daniel Holmgren, Ulf Ergander, Steven Gould, Colene Bowker, and Mario Verdicchio. 2008. "Age-and Gender-Specific Mortality Rates in Childhood Hypertrophic Cardiomyopathy." *European heart journal* 29: 1160-67.
- Owoeye, Oluwatoyosi BA. 2010. "Pattern and Management of Sports Injuries Presented by Lagos State Athletes at the 16 Th National Sports Festival (Kada Games 2009) in Nigeria." *BMC Sports Science, Medicine and Rehabilitation* 2: 3.
- Patil, Harshal R, James H O'Keefe, Carl J Lavie, Anthony Magalski, Robert A Vogel, and Peter A McCullough. 2012. "Cardiovascular Damage Resulting from Chronic Excessive Endurance Exercise." *Mo Med* 109: 312-21.
- Pelliccia, Antonio, Franco Culasso, Fernando M Di Paolo, and Barry J Maron. 1999. "Physiologic Left Ventricular Cavity Dilatation in Elite Athletes." *Annals of internal medicine* 130: 23-31.
- Pelliccia, Antonio, Robert Fagard, Hans Halvor Bjørnstad, Aris Anastassakis, Eloisa Arbustini, Deodato Assanelli, Alessandro Biffi, Mats Borjesson, François Carrè, and

- Domenico Corrado. 2005. "Recommendations for Competitive Sports Participation in Athletes with Cardiovascular Disease." *European heart journal* 26: 1422-45.
- Pelliccia, Antonio, Barry J Maron, Franco Culasso, Antonio Spataro, and Giovanni Caselli. 1996. "Athlete's Heart in Women: Echocardiographic Characterization of Highly Trained Elite Female Athletes." *Jama* 276: 211-15.
- Pelliccia, Antonio, Barry J Maron, Fernando M Di Paolo, Alessandro Biffi, Filippo M Quattrini, Cataldo Pisicchio, Alessandra Roselli, Stefano Caselli, and Franco Culasso. 2005. "Prevalence and Clinical Significance of Left Atrial Remodeling in Competitive Athletes." *Journal of the American College of Cardiology* 46: 690-96.
- Pfister, Glen C, James C Puffer, and Barry J Maron. 2000. "Preparticipation Cardiovascular Screening for Us Collegiate Student-Athletes." *Jama* 283: 1597-99.
- Puranik, Rajesh, Clara K Chow, Johan A Duflou, Michael J Kilborn, and Mark A McGuire. 2005. "Sudden Death in the Young." *Heart Rhythm* 2: 1277-82.
- Ramaraj, R. 2008. "Hypertrophic Cardiomyopathy: Etiology, Diagnosis, and Treatment." *Cardiol Rev* 16: 172-80.
- Reardon, Claudia L, and Shane Creado. 2014. "Drug Abuse in Athletes." *Subst Abuse Rehabil* 5: 95-105.
- Reimers, Carl D, G Knapp, and Anne Kerstin Reimers. 2012. "Does Physical Activity Increase Life Expectancy? A Review of the Literature." *Journal of aging research* 2012.
- Reisdorff, Earl J, and Robert J Proding. 1998. "Sudden Cardiac Death in the Athlete." *Emergency medicine clinics of North America* 16: 281-94.
- Rich, Brent SE. 1994. "Sudden Death Screening." *Medical Clinics of North America* 78: 267-88.
- Risgaard, Bjarke, Bo Gregers Winkel, Reza Jabbari, Charlotte Glinge, Ole Ingemann-Hansen, Jørgen Lange Thomsen, Gyda Lolk Ottesen, Stig Haunsø, Anders Gaarsdal Holst, and Jacob Tfelt-Hansen. 2014. "Sports-Related Sudden Cardiac Death in a Competitive and a Noncompetitive Athlete Population Aged 12 to 49 Years: Data from an Unselected Nationwide Study in Denmark." *Heart Rhythm* 11: 1673-81.
- Roberts, Robert, and Ramon Brugada. 2003. "Genetics and Arrhythmias." *Annual review of medicine* 54: 257-67.
- Rothmier, Justin D, and Jonathan A Drezner. 2009. "The Role of Automated External Defibrillators in Athletics." *Sports health* 1: 16-20.
- Semsarian, Christopher, Jodie Ingles, Martin S Maron, and Barry J Maron. 2015. "New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy." *Journal of the American College of Cardiology* 65: 1249-54.
- Sharma, Alok, Monica Colvin-Adams, and Clyde W Yancy. 2014. "Heart Failure in African Americans: Disparities Can Be Overcome." *Cleve Clin J Med* 81: 301-11.
- Sharma, S. 2003. "Athlete's Heart--Effect of Age, Sex, Ethnicity and Sporting Discipline." *Exp Physiol* 88: 665-9.

- Sharma, Sanjay. 2003. "Physiological Society Symposium—the Athlete's Heart." *Experimental Physiology* 88: 665-69.
- Sheppard, Mary N. 2012. "Aetiology of Sudden Cardiac Death in Sport: A Histopathologist's Perspective." *British journal of sports medicine* 46: i15-i21.
- Shirley, Kelly W, and Terry A Adirim. 2005. "Sudden Cardiac Death in Young Athletes." *Clinical Pediatric Emergency Medicine* 6: 194-99.
- Solberg, Erik Ekker, M Borjesson, S Sharma, M Papadakis, Matthias Wilhelm, JA Drezner, KG Harmon, JM Alonso, H Heidbuchel, and D Dugmore. 2016. "Sudden Cardiac Arrest in Sports—Need for Uniform Registration: A Position Paper from the Sport Cardiology Section of the European Association for Cardiovascular Prevention and Rehabilitation." *European journal of preventive cardiology* 23: 657-67.
- Sweeting, Joanna, Jodie Ingles, Kylie Ball, and Christopher Semsarian. 2016. "Sudden Deaths During the Largest Community Running Event in Australia: A 25-Year Review." *International journal of cardiology* 203: 1029.
- Sweeting, Joanna, and Christopher Semsarian. 2016. "Sudden Cardiac Death in Athletes: Still Much to Learn." *Cardiology Clinics* 34: 531-41.
- Tabib, A, A Miras, P Taniere, and R Loire. 1999. "Undetected Cardiac Lesions Cause Unexpected Sudden Cardiac Death During Occasional Sport Activity. A Report of 80 Cases." *European Heart Journal* 20: 900-03.
- Talbot, Laura A, Christopher H Morrell, E Jeffrey Metter, and Jerome L Fleg. 2002. "Comparison of Cardiorespiratory Fitness Versus Leisure Time Physical Activity as Predictors of Coronary Events in Men Aged \leq 65 Years and $>$ 65 Years." *The American journal of cardiology* 89: 1187-92.
- Thiene, Gaetano, Elisa Carturan, Domenico Corrado, and Cristina Basso. 2010. "Prevention of Sudden Cardiac Death in the Young and in Athletes: Dream or Reality?" *Cardiovascular Pathology* 19: 207-17.
- Thiene, Gaetano, Domenico Corrado, and Cristina Basso. 2007. "Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia." *Orphanet journal of rare diseases* 2: 45.
- Thiene, Gaetano, Andrea Nava, Domenico Corrado, Lino Rossi, and Natale Pennelli. 1988. "Right Ventricular Cardiomyopathy and Sudden Death in Young People." *New England Journal of Medicine* 318: 129-33.
- Trivax, Justin E, and Peter A McCullough. 2012. "Phidippides Cardiomyopathy: A Review and Case Illustration." *Clinical cardiology* 35: 69-73.
- Van Camp, Steven P, Colin M Bloor, Frederick O Mueller, ROBERT C Cantu, and Harold G Olson. 1995. "Nontraumatic Sports Death in High School and College Athletes." *Medicine and Science in Sports and Exercise* 27: 641-47.
- Varró, András, and István Baczkó. 2010. "Possible Mechanisms of Sudden Cardiac Death in Top Athletes: A Basic Cardiac Electrophysiological Point of View." *Pflügers Archiv-European Journal of Physiology* 460: 31-40.

- Virmani, Renu, Allen P Burke, and Andrew Farb. 2001. "Sudden Cardiac Death." *Cardiovascular pathology* 10: 211-18.
- Wheeler, Matthew T, Paul A Heidenreich, Victor F Froelicher, Mark A Hlatky, and Euan A Ashley. 2010. "Cost-Effectiveness of Preparticipation Screening for Prevention of Sudden Cardiac Death in Young Athletes." *Annals of Internal Medicine* 152: 276-86.
- Wichter, Thomas, Gerhard Hindricks, Hartmut Lerch, Peter Bartenstein, Martin Borggrefe, Otmar Schober, and Gunter Breithardt. 1994. "Regional Myocardial Sympathetic Dysinnervation in Arrhythmogenic Right Ventricular Cardiomyopathy. An Analysis Using 123i-Meta-Iodobenzylguanidine Scintigraphy." *Circulation* 89: 667-83.
- Wight, Joseph N, and Deeb Salem. 1995. "Sudden Cardiac Death and Theathlete's Heart'." *Archives of internal medicine* 155: 1473-80.

Chapter 5

SUDDEN CARDIAC DEATH IN PATIENTS WITH CONGENITAL HEART DISEASE

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ABSTRACT

Adult patients with congenital heart disease are at risk of sudden cardiac death caused by malignant ventricular tachyarrhythmias. The reported prevalence of ventricular tachyarrhythmias is up to 30% and they are mainly reported in patients with tetralogy of Fallot (ToF) and transposition of the great arteries (TGA). These dysrhythmias may be preceded by non-sustained ventricular tachycardia.

The aim of this chapter is to discuss the present knowledge on epidemiology and physiology of malignant ventricular tachyarrhythmias in patients with congenital heart disease and to demonstrate data concerning the time course of ventricular tachyarrhythmia in a large cohort of patients with a variety of congenital heart defects. In addition, the interrelationship between ventricular premature beats, (non)-sustained ventricular tachycardias and ventricular fibrillation are described. In our data, we show that ventricular tachyarrhythmias appear on average at the age of 40, but they rarely developed in patients with only non-sustained ventricular tachycardias.

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ABBREVIATIONS

ASD	atrial septal defect
AFL	atrial flutter
AVCB	atrioventricular conduction block
AVRT	atrioventricular reentrant tachycardias
AVNRT	atrioventricular nodal reentrant tachycardias
AVSD	atrioventricular septal defect
ccTGA	congenitally corrected transposition of the great arteries
CHD	congenital heart defect
CoA	coarctation of the aorta
FAT	focal atrial tachycardias
HF	heart failure
IART	intra-atrial reentrant tachycardias
PA	pulmonary atresia
PDA	patent ductus arteriosus
SCD	sudden cardiac death
SVT	supraventricular tachycardias
TA	tricuspid atresia
Tar	truncus arteriosus
TGA	transposition of the great arteries
TOF	tetralogy of Fallot
UVH	univentricular heart
VSD	ventricular septal defect
VT	ventricular tachycardia
VTA	ventricular tachyarrhythmias (VT and VF)
VF	ventricular fibrillation

INTRODUCTION

Patients with congenital heart defects (CHD) nowadays age as a result of improved long-term survival provided by advances in surgical technologies and post-operative care. This improvement in survival is complicated by the development of brady- and tachyarrhythmias, which may result in sudden cardiac death (SCD). In this chapter, we report on the present knowledge of the epidemiology and pathophysiology of SCD in CHD patients, evaluate the long-term outcomes of implantable cardioverter defibrillator (ICD) therapy, and we discuss the role of ICD therapy in the prevention of SCD.

Incidence and Prevalence of Congenital Heart Disease

Of all major congenital anomalies, nearly a third is comprised of CHD (van der Linde et al. 2011). CHD is defined as “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance”, as proposed by Mitchel et al. in the early ‘70’s (Mitchell et al. 1971).

According to the PACES/HRS Expert Consensus, CHD are often categorized in simple, moderate and severe/complex CHD (Khairy et al. 2014). This categorization is partly based on the complexity of the needed medical care of the patient rather than the anatomical complexity of defect itself and also on some surgical procedures. Till this day, there is no categorization based on anatomical complexity of the defect regarding prognoses.

Although incidences of CHD vary between continents, countries and ethnicities, an estimated overall birth prevalence of 9 per 1,000 live births is presumed, based on reports of the past 20 years (van der Linde et al. 2011). Reported birth prevalence has increased over the past few decades, which for the greater part is likely the result of improved diagnostic tools and more structural documentation of incidences, rather than it representing a true increase in the incidence of CHD. However, maternal age has also increased over the past decades, which consequently increases the risk of congenital abnormalities (van der Linde et al. 2011). Furthermore, there now is an adult population of CHD patients in improved health, whose children will have an increased risk of congenital disorders (van der Linde et al. 2011).

In addition, prevalence of CHD differs between ethnicities. CHD is less prevalent among African-Americans (Correa-Villasenor et al. 1991) and more prevalent among Asians (van der Linde et al. 2011). Also, Caucasian children appear to have more left ventricular obstructions, whereas Asian children have more right ventricular outflow tract lesions (Jacobs et al. 2000, van der Linde et al. 2011).

Non-inherited risk factors for CHD include maternal pre-gestational diabetes mellitus, phenylketonuria, febrile illness, infectious diseases, various therapeutic drug exposures, vitamin A usage, marijuana usage and exposure to organic solvents (Jenkins et al. 2007). High exposure to ionizing radiation, for instance due to professional occupation, did not show any associations with CHD birth prevalence (Jenkins et al. 2007).

Incidences of CHD subtypes separately are generally hard to assess on large scale. However, some original studies and meta-analyses comprising large populations have been performed. An overview of reported incidences of CHD subtypes of 4 of these studies is presented in Table 1 (van der Linde et al. 2011, Mitchell et al. 1971, Egbe et al. 2014, Hoffman et al. 2002).

Table 1. Reported incidences of CHD subtypes

Author	Mitchell et al.	Egbe et al.	Hofman et al.	Van der Linde et al.
Type of publication	Original research	Original research	Meta-analysis, 62 studies published since 1955	Meta-analysis, 114 studies, no time restriction
Year of publication	1970	2014	2002	2011
N population	56,109 live births	2,409,774 live births	Not reported	24,091,867 live births
CHD	Incidence per 1,000 live births			
MI	0.05	-	-	-
AS	0.28	-	0.40	0.22
PS	0.66	-	0.73	0.50
PDA	0.62	-	0.80	0.87
ASD	0.61(<i>secundum</i>)	-	0.94	1.64
VSD	2.37	-	3.57	2.62
AVSD	-	-	0.35	-
Coronary artery anomaly	0.12	-	-	-
TAPVR		0.08	0.09	-
CoA	0.41	-	0.41	0.34
Ebstein	-	0.08	0.11	-
IAA	-	0.11	-	-
TOF	0.29	0.24	0.42	0.34
DORV	0.09	0.16	0.16	-
MA	0.27	-	-	-
PA	0.12	0.08	0.13	-
TA	0.09	0.10	0.08	-
TGA	0.20	0.21	0.32	0.31
ccTGA	-	0.04	-	-
Tar	0.16	0.14	0.11	-
Single ventricle	0.07	0.05	0.11	-
HLHS	-	0.08	0.27	-
HRHS	-	-	0.22	-

ASD: atrial septal defect; AS: aortic stenosis; AVSD: atrioventricular septal defect; CoA: coarctation of the aorta; CHD: congenital heart disease; IAA: interrupted aortic arch; MA: mitral atresia; MI: mitral insufficiency; PA: pulmonary atresia; PDA: patent ductus arteriosus; PS: pulmonary stenosis; VSD: ventricular septal defect; TA: tricuspid atresia; TAPVR: total anomalous pulmonary venous return; Tar: truncus arteriosus; TOF: tetralogy of Fallot; DORV: double outlet right ventricle; (cc)TGA: (congenitally corrected) transposition of the great arteries; HLHS: hypoplastic left heart syndrome; HRHS: hypoplastic right heart syndrome.

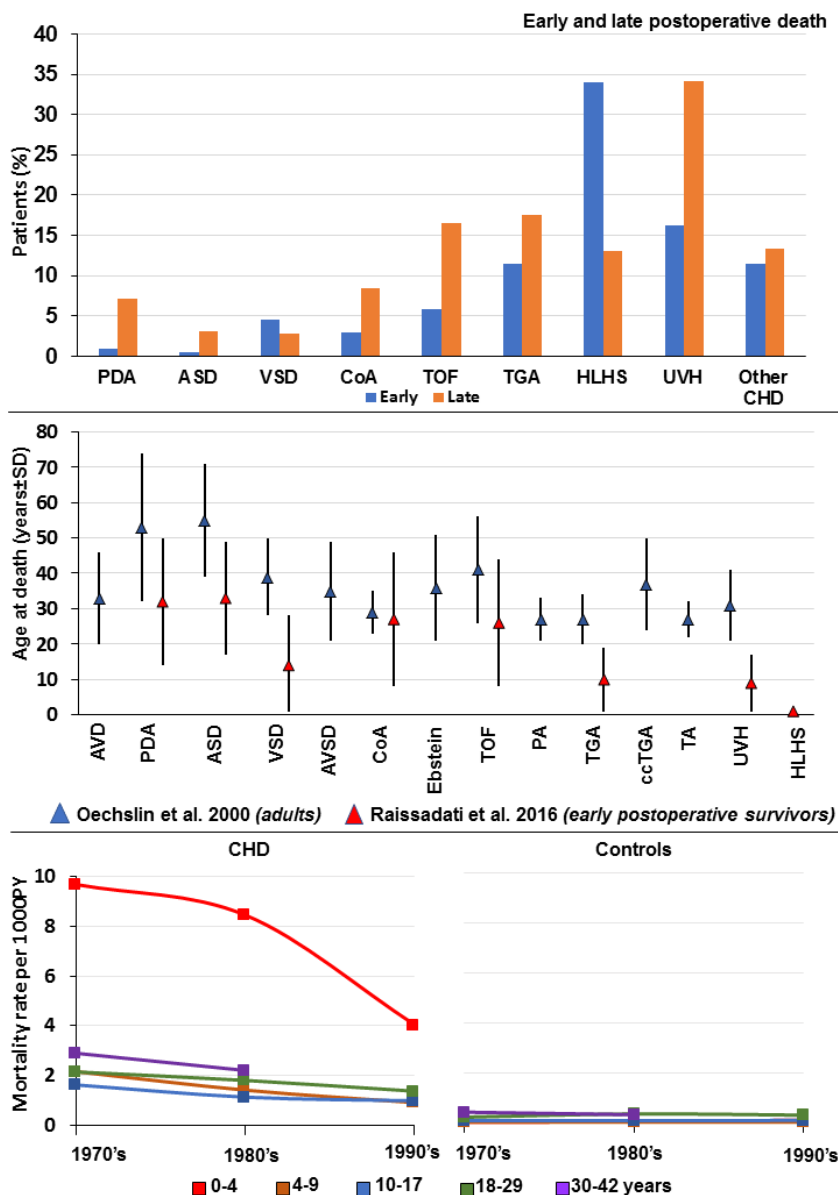


Figure 1. *Upper panel*: early and late postoperative death among CHD subtypes in a Finnish population of 10,964 CHD patients operated between 1953 and 2009 examined by Raissadati et al. in 2016. Early death is particularly prevalent in those with severe CHD. Further details are provided in paragraph ‘‘Life expectancy and quality of life of CHD patients’’. *Middle panel*: Mean age at death per CHD subtype as examined by Oechslin et al. and Raissadati et al. (Oechslin et al. 2000, Raissadati et al. 2016). *Lower panel*: mortality rates per age category of 21,982 Swedish CHD patients born between 1970 till 1993 and their matched controls examined by Mandalenakis et al. (Mandalenakis et al. 2016). ASD = atrial septal defect; AVD = aortic valve disease; AVSD = atrioventricular septal defect; ccTGA = congenitally corrected transposition of the great arteries; CHD = congenital heart defect; CoA = coarctation of the aorta; Ebstein = Ebstein’s anomaly; PDA = patent ductus arteriosus; PA = pulmonary atresia; TA = tricuspid atresia; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect.

Life Expectancy and Quality of Life of CHD Patients

At this moment, 90% of CHD patients is expected to survive into adulthood in high income countries. Data on life expectancy of all CHD subtypes separately are scarce. However, median age of survival for patients with *simple* CHD is presumed comparable to that of healthy peers. Median age of death in patients with *moderate* CHD is approximately 55 years and of those with *severe* CHD 35-40 years (Khairy et al. 2014). As shown in the upper panel of Figure 1, early and late postoperative death incidences differ between CHD subtypes, in which early death is considerably higher in those with severe CHD and even outnumber late death in patients with hypoplastic left heart syndrome (Raissadati et al. 2016).

Few studies have investigated age at death for CHD subtypes, which generally report considerably different outcomes due to methodological differences; Oechslin et al. and Raissadati et al. both reported mean age at death for several CHD subtypes, which are represented in the middle panel of Figure 1 (Raissadati et al. 2016, Oechslin et al. 2000). Where Oechslin et al. reported age at death in an adult CHD population, Raissadati et al. included all CHD patients who survived the early postoperative phase (Raissadati et al. 2016, Oechslin et al. 2000). This methodological discrepancy already comes along with a difference in survival up to 25 years in, for instance, VSD patients (Raissadati et al. 2016, Oechslin et al. 2000).

In CHD children, severity of the defect and surgical outcome are main determinants of survival. When survived to adulthood, pulmonary hypertension, heart failure, supraventricular tachycardias (SVT) and ventricular tachyarrhythmias (VT) become important factors influencing survival rates (Khairy et al. 2014).

Recently, a large case control study on CHD mortality was performed in 21,982 Swedish CHD patients born between 1970 and 1993 who were followed till 2011 (Mandalenakis et al. 2016).

The lower panel of Figure 1 gives an overview of the mortality rate per age category for CHD patients and their matched controls. Overall survival till 5 years of age was 98% for those born between 1990 and 1993 (Mandalenakis et al. 2016). Mortality risk of CHD patients was over 16 times higher than in matched controls and was highest in the first 5 years of life (Mandalenakis et al. 2016).

As expected, mortality was highest in patients with more severe CHD, including tricuspid atresia (TA), transposition of the great arteries (TGA), univentricular hearts (UVH), hypoplastic left heart syndrome, tetralogy of Fallot (TOF) and atrioventricular septal defect (AVSD), obtaining an overall incidence of death of 25% and a hazard ratio of 64 compared to control patients (Mandalenakis et al. 2016). Incidence of death in patients with atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), coarctation of the aorta (CoA) and Morbus Ebstein was 5% with a hazard ratio of 11 compared to control patients (Mandalenakis et al. 2016). In patients

with valvular malformations, a mortality of 5% was observed with a hazard ratio of 8.5 compared to controls (Mandalenakis et al. 2016).

As life expectancy of CHD patients has improved and is currently still improving, quality of life becomes more important. So far, studies on quality of life in CHD patients show conflicting results. Recently, a matched case control study has been performed in 150 adult CHD patients, reporting a higher frequency of mental disorders (Westhoff-Bleck et al. 2016). Particularly mood and anxiety disorders, including major depressive disorders, dysthymia and generalized anxiety disorders, were more prevalent in adult CHD patients (Westhoff-Bleck et al. 2016). In addition, this study was the first to take substance abuse and eating disorders into account (Westhoff-Bleck et al. 2016). Although they found slightly higher rates in CHD patients than in the control group, no statistical difference was observed (Westhoff-Bleck et al. 2016). Presence of mental disorders, particularly depression, anxiety and substance abuse, resulted in a reduction of perceived quality of life (Westhoff-Bleck et al. 2016).

Only few studies have been performed on the estimated life expectancy of CHD patients themselves. Reid et al. performed a study in which CHD patients estimated their own life expectancy and that of healthy peers, and rated their health status (Reid et al. 2006). CHD patients estimated their life expectancy to be 75 years, which was estimated 4 years shorter than that of healthy peers (Reid et al. 2006). Hence, a large overestimation of life expectancy was present. Patients with complex CHD overestimated their life expectancy with approximately 35 years and patients with moderate CHD with about 20 years (Reid et al. 2006). Overestimation of life expectancy occurred in over 85% of patients (Reid et al. 2006). Given these results, only an alarmingly small proportion of adult CHD patients have realistic views of their life expectancy. This observation emphasizes the importance for CHD specialists to provide thorough information about life expectancy and future prospects to CHD patients and, if necessary, to arrange proper guidance or coaching for this matter.

Other Causes of Death among CHD Patients

Mode of death in adult CHD patients has been investigated in a limited number of studies. In addition, comparing studies to each other can be challenging due to different categorizations of CHD subtypes, methodological protocols, follow-up duration and so on.

An overview of reported modes of death in several large CHD cohorts is presented in Figure 2. Incidences of causes of death vary between studies and include SCD (13% to 28%); progressive heart failure (HF) (21% to 28%); early perioperative death (7% to 18%); other cardiovascular diseases (8% to 19%); non- cardiovascular diseases (17% to 23%) and non-CHD related causes (18% to 36%) (Raissadati et al. 2016, Zomer et al.

2011, Oechslin et al. 2000, Engelings et al. 2016). The latter included respiratory, neurological and infectious diseases which all are more prevalent in CHD patients than in the general population (Raissadati et al. 2016). Also, alcohol related death and death due to accidents occur more among CHD patients (Raissadati et al. 2016). Suicide rates are similar for CHD patients and the general population (Raissadati et al. 2016).

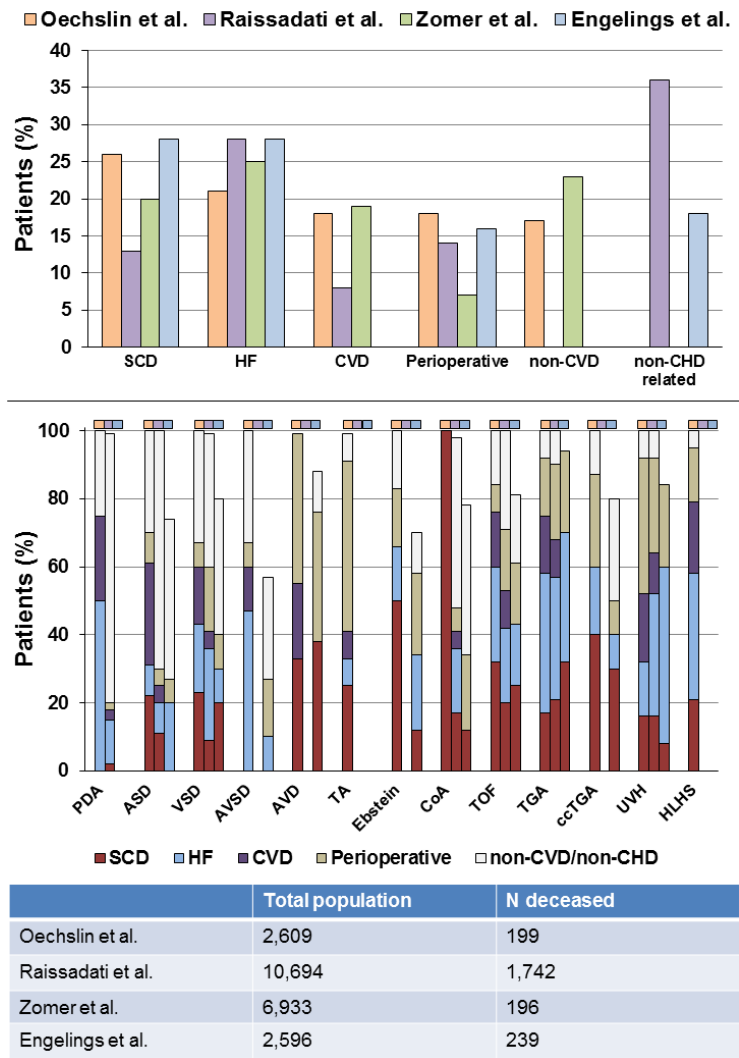


Figure 2. Upper panel: incidence of causes of death among CHD populations. Middle panel: distribution of causes of death within CHD subtypes as reported by Oechslin et al., Raissadati et al. and Engelings et al. (Engelings et al. 2016, Oechslin et al. 2000, Raissadati et al. 2016). Colored squares above the bars are conform the upper panel. Numerical data per study population is provided. ASD = atrial septal defect; AVD = aortic valve disease; AVSD = atrioventricular septal defect; ccTGA = congenitally corrected transposition of the great arteries; CHD = congenital heart defect; CoA = coarctation of the aorta; CVD= cardiovascular disease; Ebstein = Ebstein’s anomaly; HF= heart failure; HLHS= hypoplastic left heart syndrome; PDA = patent ductus arteriosus; PA = pulmonary atresia; SCD=sudden cardiac death; TA = tricuspid atresia; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect.

Incidence and Risk Factors of Sudden Cardiac Death

As a result of the tremendous improvement in diagnostic tools and surgical techniques over the past decades, the population of adult CHD patients is increasing. Currently, adult CHD patients are even outnumbering CHD infants (Khairy et al. 2014).

The improvements in healthcare have significantly increased the life expectancy of CHD patients. Yet, it also has a flipside: the aging and growing population of CHD patients often undergoes multiple surgical procedures throughout life, needs long-term expert medical care and has an increased risk of arrhythmias.

In CHD patients, arrhythmias are the main reason for hospital admission and are even a leading cause of death (Khairy et al. 2014). CHD subtypes and their risk of various S(VT) are presented in Table 2. There are three main categories of CHD patients that account for the majority of observed (S)VT, including patients who underwent a Mustard or Senning procedure, Fontan procedure and patients with repaired TOF (Triedman 2002).

The absolute incidence of SCD in a CHD patient is approximately 0.1% per year. A large population based study among 10,964 adult CHD patients performed by Raissadati et al. revealed a 40-year freedom from sudden death of 99% (95% CI: 98.5% to 99.5%) after surgery for *simple defects* and 91% (95% CI: 90% to 92%) after surgery for *severe defects* (severe vs. simple HR: 9.9; 95% CI: 6.7 to 14.6; $p < 0.0001$) (Raissadati et al. 2016). The incidence and hazard for sudden death decreased to zero among patients with ASD, VSD, TOF, and TGA that underwent surgery between 1990 and 2009. (Raissadati et al. 2016) In TOF patients, reported incidences in a total of 2,016 patients during a median follow up period of 24.6 years ranged from 2.6 to 6% (Murphy et al. 1993, Nollert et al. 1997, Silka et al. 1998, Norgaard et al. 1999, Gatzoulis et al. 2000, Khairy et al. 2008, Khairy et al. 2014). In patients with a Fontan circulation, a recent study reported that 13% of the 180 Fontan patients had SCD at an average age of 28 (23-36) years during a long-term follow-up period of 22 years (Pundi et al. 2016).

CHD associated with the highest risk on late SCD are TOF, TGA, congenitally corrected transposition of the great arteries (ccTGA), aortic stenosis (AS) and UVH. Risk factors associated with development of ventricular tachyarrhythmias (VTA: VT and ventricular fibrillation (VF)) in patients with CHD in general include depressed cardiac function, widening of the QRS complex (≥ 180 ms), the presence of SVT, systemic atrioventricular regurgitation, ageing, multiple surgical procedures and the presence of fragmented QRS complexes (fQRS) on the surface electrocardiogram.

Vogels et al. examined the occurrence of fQRS in patients with various types of CHD and evaluated whether fQRS is associated with development of VT (Vogels et al. 2017). The study group consisted of 139 (54% male) patients with VT and 219 matched controls. The criteria applied for identification of fQRS and an example of fQRS in a patient with repaired TOF is demonstrated in Figure 3. In this study, the presence of

fQRS was higher in CHD patients who developed VTA compared to matched control CHD patients without VTA. Based on their findings, the author suggested that fQRS could be used as a surrogate marker in addition to the known clinical variables (QRS prolongation, a higher number of surgical procedures and non-systemic ventricular dysfunction) to predict development of VTA in CHD patients more accurately.

Table 2. Atrial and ventricular tachyarrhythmias in CHD patients

	Risk			Estimated prevalence		Specific atrial tachyarrhythmias
	SVT	AF	VT	SVT/AF	VT	
CHD						
PDA						
PS						
VSD						
ASD <i>sec.</i>				16-28%	<2%	IART/AF
CoA						
APVR						
AVSD				5-10%	<2%	IART/AF
AS						
Ebstein				33-60%	>2%	IART; AV or atriofascicular (Mahaim)AP (SD if multiple AP); ectopic AT; AF
TOF				15-25%	10-15%	IART; NAFAT
ASD <i>prim.</i>						IART/AF
Tar				>25%	>2%	
PA						
DORV						
TGA				Atrial switch: 26-50% Arterial switch: <2%	7-9% 1-2%	IART; NAFAT; AVNRT; VT/VF
ccTGA				>30%	>2%	AP in case Ebstein-like systemic atrioventricular valve
HLHS						
Single ventricle				40-60%	>5%	IART; NAFAT; AF

AF: atrial fibrillation; AP: accessory pathway; APVR: anomalous pulmonary venous return; AS: aortic stenosis; ASD: atrial septal defect, *prim.*: *primum*, *sec.*: *secundum*; AVNRT: atrioventricular nodal reentrant tachycardia; AVSD: atrioventricular septal defect; CHD: congenital heart disease; CoA: coarctation of the aorta; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; IART: intraatrial reentrant tachycardia; NAFAT: non automatic focal atrial tachycardia; PA: pulmonary atresia; PDA: patent ductus arteriosus; PS: pulmonary stenosis; SVT: supraventricular tachycardia; Tar: truncus arteriosus; (cc)TGA: (congenitally corrected) transposition of the great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect; VT: ventricular tachycardia. Modified from Khairy P et al. (Khairy et al. 2014).

The importance of non-sustained VT as a predictor for SCD is controversial. Recently, Teuwen and Ramdjan et al. have investigated development of VTA in a cohort of 145 patients presenting with either non-sustained VT, sustained VT or VF (Figure 4) (Teuwen, Ramdjan, et al. 2016). Of the 103 patients with non-sustained VT, only a minority of 5 patients developed sustained VT or VF during a median follow-up time of 5 years. These 5 patients included 3 patients with simple defects, 1 TGA and 1 TOF patient (Teuwen, Ramdjan, et al. 2016). Khairy et al. reported the prognostic value of inducible sustained VT as independent risk factor for subsequent sustained VT and SCD in TOF patients (relative risk 4.7) (Khairy et al. 2004).

Criteria for identification of fractionated QRS complexes

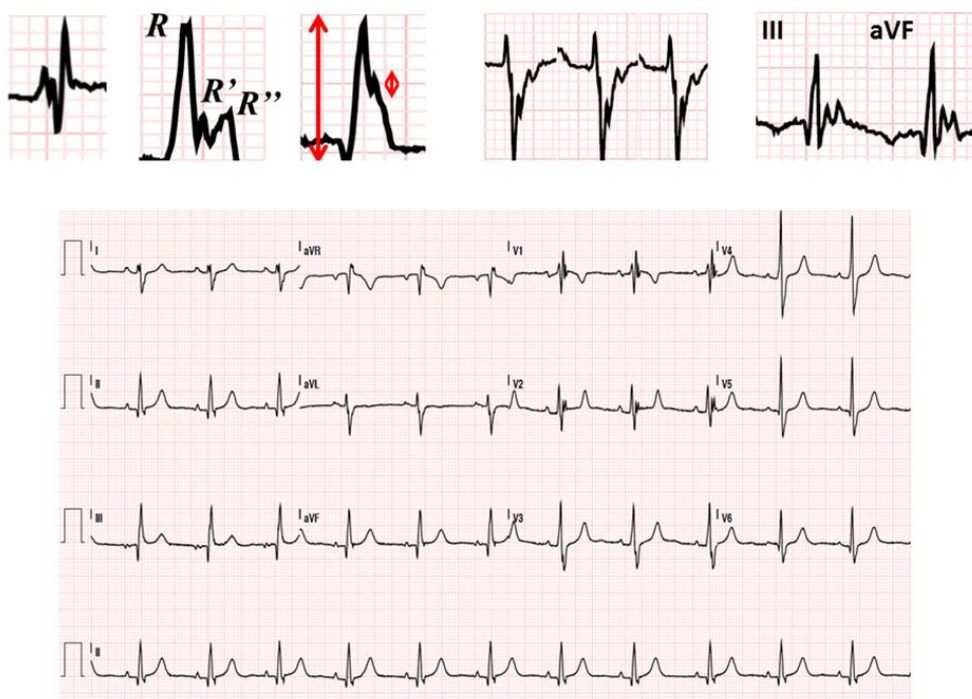


Figure 3. Upper panel: fQRS were identified by using a standard 12-lead ECG (filter range 0.05–150 Hz; AC filter 50 Hz, 25 mm/s, 10 mm/mV) and applying the following criteria: 1) a clear distinct additional deflection is visible in the R or S wave, 2) one R' or S' is present in narrow QRS complexes (<120ms), two or more R' or S' in wide QRS complexes (≥ 120 ms), 3) the proportion of RR' or SS' is 1:6 or less, 4) more than half of the QRS complexes within one lead have fQRS, 5) a maximum of two leads corresponding to a particular heart area contain fQRS. Three different areas of the heart were distinguished: inferior (II, III, aVF), anterior (V1, V2, V3, V4) and lateral (I, aVL, V5, V6). Lower panel: surface electrogram obtained from a patient with a surgically corrected tetralogy of Fallot showing fQRS.

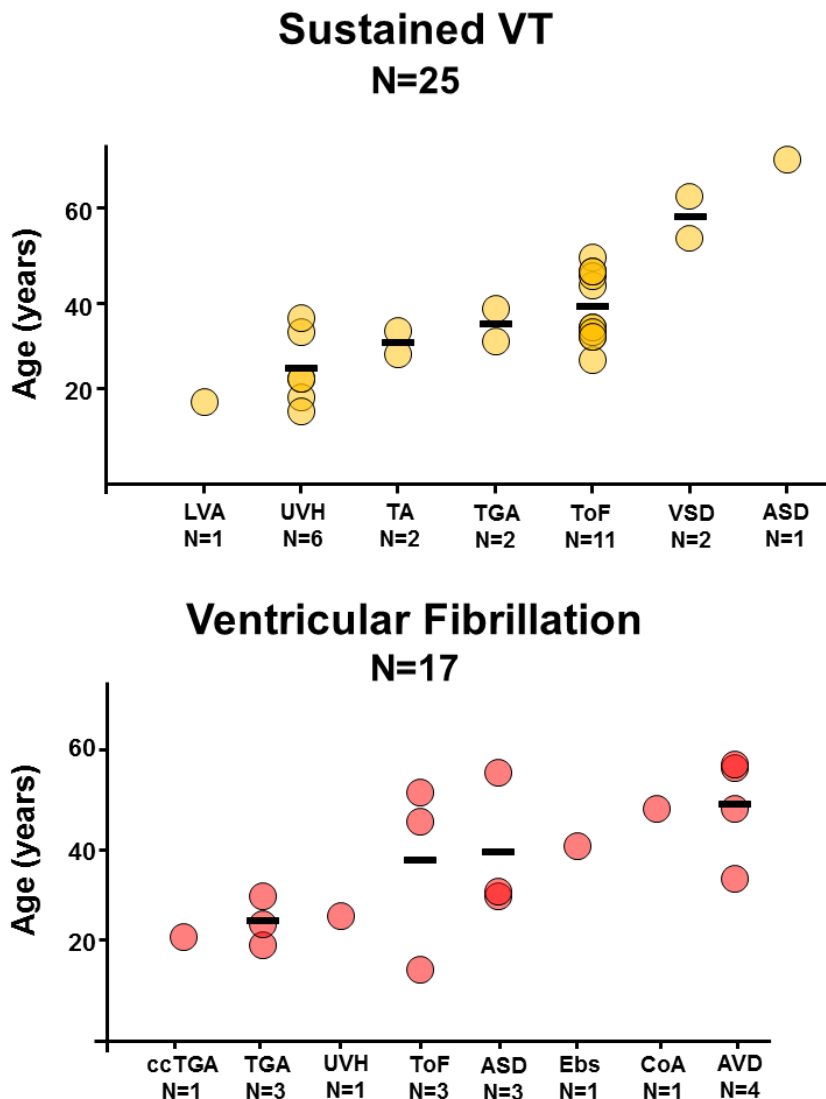


Figure 4. Age at the moment of first presentation with sustained VT (upper panel) and VF (lower panel). The horizontal bar indicates the average age in years. ASD = atrial septal defect; AVD = aortic valve disease; AVSD = atrioventricular septal defect; ccTGA = congenitally corrected transposition of the great arteries; CHD = congenital heart defect; CoA = coarctation of the aorta; Ebs = Ebstein anomaly; LVA = left ventricular aneurysm; MI = mitral valve insufficiency; PDA = patent ductus arteriosus; PS = pulmonary valve stenosis; Tar = truncus arteriosus; TGA = transposition of the great arteries; ToF = tetralogy of Fallot; UVH = univentricular heart; VSD = ventricular septal defect.

Early Postoperative (Sudden) Death

Early postoperative death (<30 days after cardiac surgery) generally occurs in a small number of patients. A large Finish cohort consisting of 10,964 CHD patients reported early postoperative death in 5.6% of the population operated between 1953 and 2009 (Raissadati et al. 2016). The upper panel of Figure 1 displays the incidence of early and

late postoperative death per CHD subtype in this population from 1953 onwards (Raissadati et al. 2016).

In the population undergoing cardiac surgery on their CHD after 1990, incidence of early postoperative death had decreased to zero for PDA and ASD patients (Raissadati et al. 2016). Early death in CoA patients remained more or less stable with an incidence of 0.29 per 1,000 person years. However, for patients with severe CHD, early mortality rates have improved substantially the past decades (Raissadati et al. 2016). From 1953 to 1989, ventricular septal defect (VSD) corrections had an early postoperative death incidence of 1.13 per 1,000 person years, whereas from 1990 onwards, early death incidence decreased to 0.34 per 1,000 person years (Raissadati et al. 2016). In TOF patients, early postoperative death diminished from 1.55 to 0.78 per 1,000 person years (Raissadati et al. 2016). Incidence of early death after TGA or UVH surgery remained relatively high with respective rates of 2.52 and 6.95 per 1,000 person years between 1990 and 2009 (Raissadati et al. 2016).

The improvement of early death rates of both TOF and VSD patients can be explained by the shift from staged procedures, in which patients were first palliated by shunts, to primary repairs. From 2000 on, primary repairs are performed in the vast majority of TOF patients and palliative shunts are rarely performed. This is also the case for VSD patients. Nowadays, primary VSD closure is the standard, whereas in previous decades pulmonary banding or reconstruction of the aortic arch was performed prior to corrective surgery.

Congenital Coronary Artery Anomalies

From the surgical point of view, congenital coronary artery abnormalities remain a subgroup with a high risk on SCD, as patients are often asymptomatic and thus often not diagnosed or not operated on. Specifically in the young, congenital coronary artery disease may cause up to 35% of SCD cases (Basso et al. 2001). Abnormalities include an anomalous origin, course or a combination of both, which will be briefly discussed.

Coronary ostia malformations consist of a plication of the aortic wall, causing a ridge that can lead to severe obstruction of the coronary ostia when it exceeds 50% of the ostial lumen. When diastolic filling or the coronary arteries is obstructed, this will lead to ischemia, giving rise to life threatening arrhythmias (Basso et al. 2001).

Anomalous coronary artery origin from the aorta is most often reported in relation to SCD. In this case, the right coronary artery originates from the left coronary sinus or vice versa. The proximal part of the coronary artery may then run anteriorly of the pulmonary trunk, posteriorly of the aorta or in between the aorta and pulmonary trunk (Basso et al. 2001). The interarterial course of the anomalous coronary is either within myocardial sulcus (intramyocardial) or within the aortic wall (intramural) (Frommelt 2009). The total prevalence of the left coronary artery originating from the right sinus Valsalva and right

coronary artery from the left sinus with an interarterial course is more than 1% of the general population (Frommelt 2009).

The anomalous left coronary artery originating from the right coronary sinus is presumed more malignant than the right coronary artery (Basso et al. 2001, Frommelt 2009). As the lumen of the former is more narrow due to its abnormal course with an acute angle, it likely results in less flow reserve and subsequent myocardial ischemia (Basso et al. 2001, Cheitlin et al. 2009, Frommelt 2009).

In addition, coronary occlusion due to systolic expansion of the aortic root and intimal damage due to the acute angle of the coronary origin causing coronary spasm during physical activity have been proposed as underlying mechanisms as well (Cheitlin et al. 2009).

An anomalous origin of the left circumflex coronary artery originating from the right coronary artery or the right coronary sinus occurs most frequently and is often an incidental finding on autopsy (Basso et al. 2001). It was considered as a benign condition, however, few case reports have been published in which no other cause for myocardial infarction or SCD could be found (Basso et al. 2001). Similarly, a high take-off of the coronary artery from the aortic wall was also considered benign, yet it was reported in one case of unexplained SCD (Basso et al. 2001).

Surgical Intervention in Coronary Artery Anomalies

In case of diagnosis of an anomalous origin of the coronary artery, several surgical interventions are possible, including patch coronary angioplasty of the coronary origin, coronary bypass, and reimplantation of the coronary (Frommelt 2009). For anomalous coronary with an intramural interarterial course, unroofing of the coronary artery and creating a new origin in the appropriate sinus is now the preferred intervention (Frommelt 2009).

There has been some debate on which patients should undergo surgical intervention and which not. Generally, surgical intervention was only performed when (symptoms indicating) myocardial ischemia were present (Class I indication) (Frommelt 2009). Symptoms of ischemia occur in approximately 50% of patients with an anomalous origin who present with SCD (Frommelt 2009). However, there is a Class II indication for any patient with an anomalous left coronary artery from the right sinus with an interarterial course, especially when the coronary artery has an intramural course (Frommelt 2009). In this case, surgical unroofing without revascularization can be performed (Frommelt 2009). On the contrary, when the coronary artery has an intramyocardial course, manipulation of the coronary artery itself is necessary and contains the risk of scarring in case of a patch angioplasty or graft failure in case of bypass grafting (Frommelt 2009).

Arrhythmic Causes of Sudden Cardiac Death

Sudden cardiac death in patients with CHD is caused by development of either complete atrioventricular conduction block, SVT or VT (Khairy et al. 2014).

Congenital atrioventricular conduction block, often referred to as congenital heart block (CHB), is defined as an atrioventricular conduction block diagnosed in utero, at birth, or within the first month of life (Baruteau et al. 2016). It occurs in approximately 1 per 15,000-20,000 live births and may occur in patients with structurally normal hearts as well as in CHD patients (Baruteau et al. 2016, Bordachar et al. 2013). CHB is regarded as a passively acquired autoimmune disease resulting from inflammatory responses eventually causing scarring of the conduction system (Baruteau et al. 2016, Bordachar et al. 2013).

Due to low nocturnal ventricular heart rates, these patients are specifically at risk for SCD during sleep (Bordachar et al. 2013). Without pacemaker therapy, mortality of CHB is high with rates of 8-16% in infants and 4-8% in children and adults. In fetuses and neonates, mortality rates of untreated patients are up to 34% (Baruteau et al. 2016, Bordachar et al. 2013).

The first presentation of CHB varies considerably, from asymptomatic to heart failure or SCD (Baruteau et al. 2016, Bordachar et al. 2013). In symptomatic patients presenting with either syncope, congestive heart failure or chronotropic incompetence, pacing therapy is warranted (Bordachar et al. 2013). However, some patients present only with complaints of tiredness or poor growth (Bordachar et al. 2013). Even if these complaints are most likely caused by bradycardia, the decision of initiating pacemaker therapy can be challenging, as long term right ventricular pacing therapy comes along with a risk of pacing induced cardiomyopathy (Baruteau et al. 2016, Bordachar et al. 2013).

Furthermore, dysfunction of the atrioventricular conduction system may occur in specific CHD subtypes, posing the risk of complete atrioventricular conduction block at some point in life. CHD subtypes that are particularly at risk are AVSD, ccTGA and left isomerism (Khairy et al. 2014). The atrioventricular node can be displaced both posteriorly and inferiorly due to malalignment of the atria and the ventricular septum (Khairy et al. 2014). In ccTGA patients, the conduction system is positioned more anteriorly and laterally and the His bundle is fragile (Khairy et al. 2014). This contains a higher risk of heart block, specifically following surgery or endovascular procedures.

Weindling et al. examined postoperative complete atrioventricular conduction block (AVCB) in patients undergoing CHD surgery and reported an incidence of 1-3%. Most often complete AVCB was transient; half of the patients showed recovery within 7-10 days (Weindling et al. 1998). A more recent study by Ayyildiz et al. reported transient and permanent complete AVCB in respectively 4% and 2% of CHD patients. Transient complete heart block recovered within 10 days in 97% of patients (Ayyildiz et al. 2016). Surgical procedures in the area of the atrioventricular node logically contain the highest

risk. This includes surgery on septal defects, surgery along the left ventricular outflow tract and surgery on left-sided valvular heart disease.

In addition to post-operative *early* AVCB, *late onset* AVCB may also occur. Liberman et al. investigated the incidence of late onset complete AVCB as the indication for pacemaker implantation among patients with various CHD. Out of 333 pacemaker implantations, 4.5% was due to late onset postoperative heart block up to 18 years after cardiac surgery (Liberman et al. 2008).

Earlier studies performed in TOF patients with transient, early postoperative AVCB and residual bifascicular block reported incidences of late onset complete AVCB up to 33% (Krongrad 1978, Wolff et al. 1972). Therefore, in these specific patients, postoperative pacemaker implantation could be considered.

Supraventricular Tachycardias

SVT are common complications late after cardiac surgery for CHD (Khairy et al. 2014). Sudden cardiac death due to SVT is assumed to be caused by rapid AVCB or hemodynamic instability and myocardial ischemia which in turn may trigger VTA. Estimated prevalences of SVT differ between CHD subtypes. As displayed in Table 2, SVT are highly prevalent in adults with UVH and Ebstein's anomaly, whereas the prevalence among TGA patients who underwent an arterial switch procedure has drastically decreased compared to those who have undergone an atrial switch procedure (Khairy et al. 2014). Almost 50% of the patients who underwent a Fontan procedure in whom the entire right atrium was connected to the pulmonary artery develop intra-atrial reentrant tachycardias (IART) within a 10 years period (Fishberger et al. 1997). Fortunately, this risk has been lowered by the introduction of the combination of a lateral right atrial tunnel and a cavopulmonary connection (Stamm et al. 2001). An estimated 50% of 20-year old CHD patients will develop SVT or atrial fibrillation (AF) during life (Bouchardy et al. 2009).

Follow-up studies of CHD patients with postoperative IART reported SCD in 10% of them; in patients who had undergone the Fontan, Mustard or Senning procedure, SCD occurred in 6% (Triedman 2002). Focal atrial tachycardias (FAT) occur less frequently and are not regarded as risk factors of SCD (de Groot et al. 2010).

Atrial macro-reentrant tachycardias, including IART and atrial flutter (AFL) are the most frequently occurring SVT in patients with both repaired and unrepaired CHD (de Groot et al. 2010, de Groot, Lukac, et al. 2009, Teuwen, Taverne, et al. 2016, Triedman 2002). IART occurs mostly in CHD patients with extensive atrial scarring (Triedman 2002). AFL are mainly observed in patients with TOF or ASD whereas IART are mainly observed in patients with UVH and TGA (de Groot et al. 2010, De Groot, Blom, et al. 2009). IART most often originate from the right atrium (de Groot et al. 2010), usually involving the right atriotomy scar, inserted prosthetic materials such as atriopulmonary conduits, intra-atrial baffles or septal patches. IART originating from the left atrium

occur less frequently and have mainly been reported in patients with ASD, TGA, UVH and TOF. Almost 50% of patients who underwent a Fontan procedure in whom the entire right atrium was connected to the pulmonary artery develop IART within a 10 years period (Fishberger et al. 1997). Fortunately, this risk has been lowered by the introduction of the combination of a lateral right atrial tunnel and a cavopulmonary connection (Stamm et al. 2001).

Reports on development of AF in patients with CHD are rare, though AF is nowadays increasingly observed due to ageing of the CHD population (De Groot, Blom, et al. 2009, Teuwen et al. 2015). So far, only one study reported on development of AF in CHD patients over time.

Teuwen et al. studied the time course of AF in 199 patients with different CHD (ASD: N = 58, AVD: N = 34, ToF: N = 21, TGA: N = 17, UVH: N = 16, VSD: N = 12, CoA: N = 9, PDA: N = 7, PS: N = 7, AVSD: N = 4, ccTGA: N = 4, Ebstein anomaly: N = 4), pulmonary atresia with VSD: N = 4, cor triatrium: N = 1, situs inversus: N = 1) and found that AF occurred at a relative young age of 49 ± 17 (15-91) years (Teuwen et al. 2015). In this study population, AF progressed from paroxysmal to persistent AF in only 3 years after the initial AF episode.

In addition, coexistence of SVT and AF occurred in one third of the patients.

Ventricular Tachyarrhythmias

VT are presumed a leading cause of SCD in CHD patients and occur more frequently in patients with CoA, TGA, TOF, AS, Ebstein and DORV (Khairy et al. 2014). However, the incidence of sustained VT in adult CHD patients is low with an estimated risk 0.1 to 0.2% per year.

VT in CHD patients are caused by macro-reentry around areas of scar tissue or suture lines created during cardiac surgery, but they may also be caused by stretch-induced automaticity or triggered activity. Additionally, the longstanding post-operative ventricular pressure/volume overload induces ventricular remodeling facilitating development of intra-ventricular conduction abnormalities and hence arrhythmias. The first-choice treatment modality for CHD patients with VT to prevent SCD is implantation of an ICD; pharmacotherapy and catheter ablation (Figure 5) (Ramdjan et al. 2015) may serve as adjunctive therapies to reduce recurrent ICD discharges.

Cardiac Surgery and Arrhythmias

In CHD patients undergoing cardiac surgery, arrhythmia surgery can be performed concomitantly and is recommended in specific cases according to the current guidelines (Khairy et al. 2014).

In adult patients undergoing Fontan conversion, a modified right atrial Maze procedure should be performed in case of symptomatic right atrial IART (Khairy et al. 2014). In addition, both the modified right atrial Maze and a left atrial Cox Maze III should be performed in these patients in case of AF episodes (Khairy et al. 2014). The left atrial Cox Maze III with ablation of the right atrial cavotricuspid isthmus may benefit CHD patients with AF, while a right atrial Maze may be beneficial in CHD patients with sustained AFL (Khairy et al. 2014).

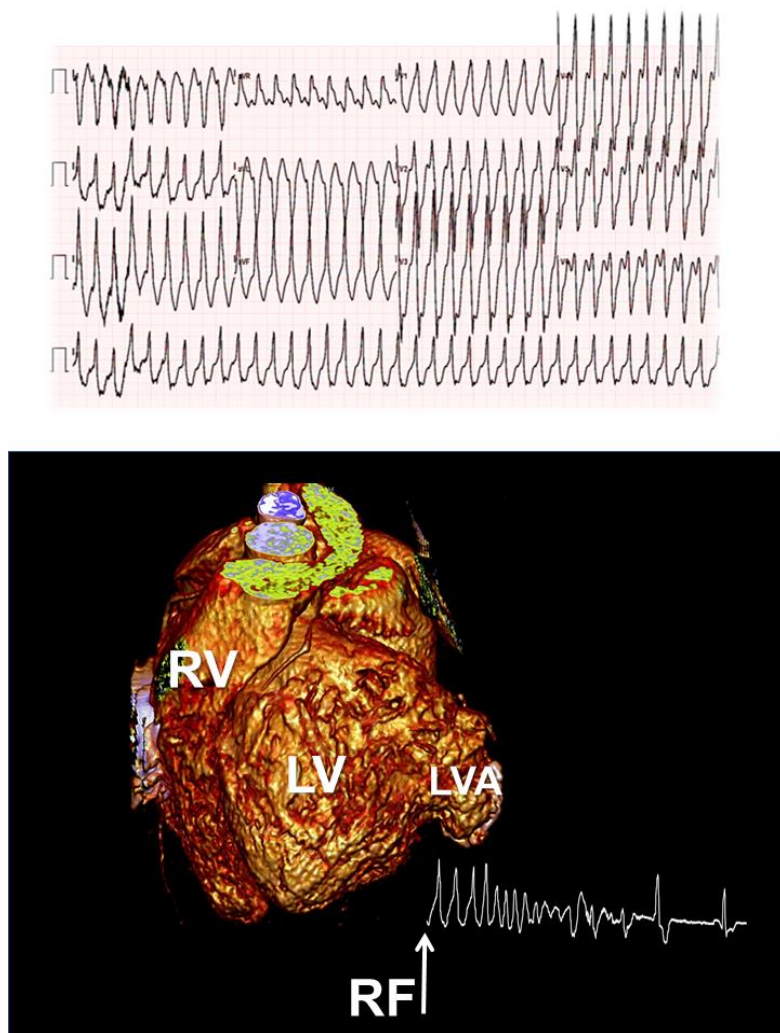


Figure 5. Catheter ablation of a VT in a 19-year-old male patient with a surgically corrected congenital left ventricular aneurysm (LVA), an ICD and recurrent VT. Surgical resection of an aneurysm in the basal posterior wall of the left ventricle was performed 10 years ago. A recurrence of the LVA was discovered during echocardiographic examination only one year after cardiac surgery. Eight years later, he developed non-sustained VT which progressed to sustained VTs within 3 years. Mapping during VT revealed the earliest activation relative to the onset of the QRS complex within the aneurysm. The VT terminated during RF application (RF). RV = right ventricle, LV = left ventricle, LVA = left ventricular aneurysm.

In case of no documentation of SVT episodes, but inducible AFL, patients may still be considered for concomitant right atrial Maze or ablation of the cavotricuspid isthmus (Khairy et al. 2014).

With regard to ventricular arrhythmias, surgical VT ablation should be considered in case a patient has sustained monomorphic VT (Khairy et al. 2014). However, when no clinical sustained VT is present, surgical VT ablation is considered reasonable when monomorphic VT is inducible (Khairy et al. 2014).

Heart Failure and Arrhythmia

Previous studies have reported ventricular ectopy in practically all patients with HF (Leier et al. 2000). During 24- and 48hr rhythm recordings, 10-15% of HF patients showed sustained VT (Leier et al. 2000). Non-sustained VT occurred in 40-80% and in over 80% of the patients had frequent premature ventricular complexes (Leier et al. 2000). Of HF populations, 30-40% of the mortality is due to SCD. SCD in HF patients is most often due to VT (Leier et al. 2000). However, bradyarrhythmias including sinus arrest and AV-block account for up to 30% of SCD, especially in those with more advanced HF (Leier et al. 2000).

In CHD patients, HF is common long term sequelae. Ventricular dyssynchrony due to ventricular conduction delay can attribute to the development of ventricular dysfunction. This is particularly a problem in patients with a postoperative right bundle branch block, which is common in patients with TOF, VSD, DORV, AVSD and Ebstein (Khairy et al. 2014). In patients with left-sided CHD, systemic left ventricular failure is frequently observed. Particularly in patients with TOF and Ebstein, left ventricular dysfunction has been associated with SCD (Khairy et al. 2014).

ICD Indications

According to the PACES/HRS guidelines (Khairy et al. 2014), ICDs are indicated in patients who 1) are survivors of a cardiac arrest due to VF or unstable VT after exclusion of reversible causes, 2) have spontaneous VT and have undergone hemodynamic and electrophysiological evaluation, or 3) have a systemic ventricular ejection fraction less than 35%, biventricular physiology, NYHA class II/III or symptoms (Class I recommendation). Implantation of an ICD may be reasonable in patients with TOF who have multiple risk factors including left ventricular systolic and diastolic dysfunction, non-sustained VT, QRS duration longer than 180 ms, extensive right ventricular scarring and inducible VT during electrophysiology study (class IIA recommendation). An ICD implantation may also be reasonable in patients with a single or systemic right ventricular ejection fraction <35%, particularly in the presence of risk factors such as VT, unexplained syncope, NYHA class II/III, QRS > 140ms, severe systemic atrio-ventricular

regurgitation, inducible VT during electrophysiology study and patients awaiting a heart transplantation (class IIB recommendation).

Outcomes of ICD Implantations

Implantation of an ICD in a CHD patient can be challenging due to the complex cardiac anatomy, abnormal systemic venous access to the ventricle or severe atrioventricular valve disease. In order to avoid invasive procedures for placement of epicardial leads, alternative approaches such as transhepatic or transatrial lead insertions have been described (Chubb and Rosenthal 2016, Chubb, O'Neill, et al. 2016, Cannon et al. 2006).

CHD patients face a life with multiple device replacements as they often receive an ICD at a relatively young age. Also, due to the long-term presence of transvenous leads, they have an increased likelihood of lead failure, venous occlusions, endocarditis and embolic vascular events, particularly in patients with intracardiac shunts.

So far, only a few studies have reported on the long-term outcome of ICD implantation in CHD patients. In a Dutch multicenter study (Yap et al. 2007), 64 adult CHD patients (37 ± 17 years; ToF (N = 40), complete TGA after atrial switch (N = 7), corrected DORV (N = 5), repaired VSD (N = 3), congenital aortic regurgitation with aortic valve replacement (N = 2), repaired CoA (N = 2), corrected ASD (N = 1), uncorrected ASD (N = 1), unrepaired double chambered right ventricle (N = 1), congenital PS with previous balloon dilatation (N = 1), uncorrected Ebstein malformation (N = 1)) were followed during a median period of 3.7 years after implantation. The incidence of both early (pocket hematoma: N = 3, lead failure: N = 2 and pneumothorax: N = 2) and late (lead failure: N = 6 and electrical storm: N = 3) complications was low. Twenty-three percent of the ICD shocks were appropriate. However, 41% of the ICD shocks occurring in 26 patients were inappropriate and were caused by SVT.

Santharam et al. also reported on the long-term outcome of 42 adult CHD patients (mean age of 45 years) with ICDs. During a 5-year follow-up period, 19 patients had complications including inappropriate shocks (N = 11), inappropriate pacing resulting in ventricular fibrillation (N = 1), infection requiring extraction (N = 1), lead failures (N = 3) and pneumothorax (N = 1) (Santharam et al. 2016). They also made a comparison between patients with TOF and other CHD and found no differences in outcomes and complications (mean age at implantation: 44.9 versus 37.7, $P = 0.10$, proportion of patients receiving an ICD for primary prevention: both groups 38%, percentage appropriate ICD shocks, TOF: 4%, others: 2%, $P = 0.66$, percentage inappropriate ICD shocks, TOF: 6%, others: 5%, $P = 1.0$) (Santharam et al. 2016). Thus, ICD therapy is effective, though associated with a high incidence of inappropriate shocks.

Data on clinical experiences with subcutaneous ICDs in CHD patients is limited. So far, only Moore et al. reported on 20 patients (21 male, median age: 33.9 years, UVH: N = 11, TGA: N = 2, TOF: N = 2, aortic valve disease: N = 2 or other biventricular surgery: N = 2) who received a subcutaneous ICD as there was limited or no transvenous access to the subpulmonary right ventricle. VT were induced in 17 patients and they were all defibrillated with less than 80 J. During the median follow up of 14 months, 1 patient received appropriate ICD shocks whereas 5 patients received inappropriate ICD shocks caused by either SVT or T wave oversensing.

CONCLUSION

SCD in CHD patients are caused by complete atrioventricular conduction block, SVT, or VT. SCD is prevented by ICD therapy, whereas both pharmacological and ablative therapy mainly serve as adjunctive treatment modalities to reduce the number of recurrent ICD discharges. ICD implantation may be challenging due to the complex cardiovascular structure and requires an individualized approach. Reports on subcutaneous ICDs are rare, yet initial results are promising. Particularly, subcutaneous ICDs offer new possibilities. Unfortunately, the long-term outcome of ICD therapy is complicated by a high incidence of inappropriate ICD discharges, primarily due to SVT. Hence, the aggressive therapy of not only VTA, but also SVT and VTA seems justified.

REFERENCES

- Ayyildiz, P., T. Kasar, E. Ozturk, I. Ozyilmaz, I. C. Tanidir, A. Guzeltas, and Y. Ergul. 2016. "Evaluation of permanent or transient complete heart block after open heart surgery for congenital heart disease." *Pacing Clin Electrophysiol* 39 (2):160-5.
- Baruteau, A. E., R. H. Pass, J. B. Thambo, A. Behaghel, S. Le Pennec, E. Perdreau, N. Combes, L. Liberman, and C. J. McLeod. 2016. "Congenital and childhood atrioventricular blocks: pathophysiology and contemporary management." *Eur J Pediatr* 175 (9):1235-48.
- Basso, C., D. Corrado, and G. Thiene. 2001. "Congenital coronary artery anomalies as an important cause of sudden death in the young." *Cardiol Rev* 9 (6):312-7.
- Bordachar, P., W. Zachary, S. Ploux, L. Labrousse, M. Haissaguerre, and J. B. Thambo. 2013. "Pathophysiology, clinical course, and management of congenital complete atrioventricular block." *Heart Rhythm* 10 (5):760-6.

- Bouchardy, J., J. Therrien, L. Pilote, R. Ionescu-Ittu, G. Martucci, N. Bottega, and A. J. Marelli. 2009. "Atrial arrhythmias in adults with congenital heart disease." *Circulation* 120 (17):1679-86.
- Cannon, B. C., R. A. Friedman, A. L. Fenrich, C. D. Fraser, E. D. McKenzie, and N. J. Kertesz. 2006. "Innovative techniques for placement of implantable cardioverter-defibrillator leads in patients with limited venous access to the heart." *Pacing Clin Electrophysiol* 29 (2):181-7.
- Cheitlin, M. D., and J. MacGregor. 2009. "Congenital anomalies of coronary arteries: role in the pathogenesis of sudden cardiac death." *Herz* 34 (4):268-79.
- Chubb, H., M. O'Neill, and E. Rosenthal. 2016. "Pacing and Defibrillators in Complex Congenital Heart Disease." *Arrhythm Electrophysiol Rev* 5 (1):57-64.
- Chubb, H., and E. Rosenthal. 2016. "Implantable cardioverter-defibrillators in congenital heart disease Implantierbare Kardioverter-Defibrillatoren bei angeborenem Herzfehler." *Herzschrittmacherther Elektrophysiol* 27 (2):95-103.
- Correa-Villasenor, A., R. McCarter, J. Downing, and C. Ferencz. 1991. "White-black differences in cardiovascular malformations in infancy and socioeconomic factors. The Baltimore-Washington Infant Study Group." *Am J Epidemiol* 134 (4):393-402.
- De Groot, N. M., J. Z. Atary, N. A. Blom, and M. J. Schalij. 2010. "Long-term outcome after ablative therapy of postoperative atrial tachyarrhythmia in patients with congenital heart disease and characteristics of atrial tachyarrhythmia recurrences." *Circ Arrhythm Electrophysiol* 3 (2):148-54.
- De Groot, N. M., N. Blom, E. E. Vd Wall, and M. J. Schalij. 2009. "Different mechanisms underlying consecutive, postoperative atrial tachyarrhythmias in a Fontan patient." *Pacing Clin Electrophysiol* 32 (11):e18-20.
- De Groot, N. M., P. Lukac, N. A. Blom, J. P. van Kuijk, A. K. Pedersen, P. S. Hansen, E. Delacretaz, and M. J. Schalij. 2009. "Long-term outcome of ablative therapy of postoperative supraventricular tachycardias in patients with univentricular heart: a European multicenter study." *Circ Arrhythm Electrophysiol* 2 (3):242-8.
- Egbe, A., S. Uppu, S. Lee, D. Ho, and S. Srivastava. 2014. "Changing prevalence of severe congenital heart disease: a population-based study." *Pediatr Cardiol* 35 (7):1232-8.
- Engelings, C. C., P. C. Helm, H. Abdul-Khaliq, B. Asfour, U. M. Bauer, H. Baumgartner, D. Kececiloglu, M. A. Korten, G. P. Diller, and O. Tutarel. 2016. "Cause of death in adults with congenital heart disease - An analysis of the German National Register for Congenital Heart Defects." *Int J Cardiol* 211:31-6.
- Fishberger, S. B., G. Wernovsky, T. L. Gentles, K. Gauvreau, J. Burnett, J. E. Mayer, Jr., and E. P. Walsh. 1997. "Factors that influence the development of atrial flutter after the Fontan operation." *J Thorac Cardiovasc Surg* 113 (1):80-6.
- Frommelt, P. C. 2009. "Congenital coronary artery abnormalities predisposing to sudden cardiac death." *Pacing Clin Electrophysiol* 32 Suppl 2:S63-6.

- Gatzoulis, M. A., S. Balaji, S. A. Webber, S. C. Siu, J. S. Hokanson, C. Poile, M. Rosenthal, M. Nakazawa, J. H. Moller, P. C. Gillette, G. D. Webb, and A. N. Redington. 2000. "Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study." *Lancet* 356 (9234):975-81.
- Hoffman, J. I., and S. Kaplan. 2002. "The incidence of congenital heart disease." *J Am Coll Cardiol* 39 (12):1890-900.
- Jacobs, E. G., M. P. Leung, and J. Karlberg. 2000. "Distribution of symptomatic congenital heart disease in Hong Kong." *Pediatr Cardiol* 21 (2):148-57.
- Jenkins, K. J., A. Correa, J. A. Feinstein, L. Botto, A. E. Britt, S. R. Daniels, M. Elixson, C. A. Warnes, C. L. Webb, and Young American Heart Association Council on Cardiovascular Disease in the. 2007. "Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics." *Circulation* 115 (23):2995-3014.
- Khairy, P., L. Harris, M. J. Landzberg, S. Viswanathan, A. Barlow, M. A. Gatzoulis, S. M. Fernandes, L. Beauchesne, J. Therrien, P. Chetaille, E. Gordon, I. Vonder Muhll, and F. Cecchin. 2008. "Implantable cardioverter-defibrillators in tetralogy of Fallot." *Circulation* 117 (3):363-70.
- Khairy, P., M. J. Landzberg, M. A. Gatzoulis, H. Lucron, J. Lambert, F. Marcon, M. E. Alexander, and E. P. Walsh. 2004. "Value of programmed ventricular stimulation after tetralogy of fallot repair: a multicenter study." *Circulation* 109 (16):1994-2000.
- Khairy, P., G. F. Van Hare, S. Balaji, C. I. Berul, F. Cecchin, M. I. Cohen, C. J. Daniels, B. J. Deal, J. A. Dearani, Nd Groot, A. M. Dubin, L. Harris, J. Janousek, R. J. Kanter, P. P. Karpawich, J. C. Perry, S. P. Seslar, M. J. Shah, M. J. Silka, J. K. Triedman, E. P. Walsh, and C. A. Warnes. 2014. "PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD)." *Heart Rhythm* 11 (10):e102-65.
- Krongrad, E. 1978. "Prognosis for patients with congenital heart disease and postoperative intraventricular conduction defects." *Circulation* 57 (5):867-70.
- Leier, C. V., R. J. Alvarez, and P. F. Binkley. 2000. "The problem of ventricular dysrhythmias and sudden death mortality in heart failure: the impact of current therapy." *Cardiology* 93 (1-2):56-69.
- Liberman, L., R. H. Pass, A. J. Hordof, and H. M. Spotnitz. 2008. "Late onset of heart block after open heart surgery for congenital heart disease." *Pediatr Cardiol* 29 (1):56-9.

- Mandalenakis, Z., A. Rosengren, K. Skoglund, G. Lappas, P. Eriksson, and M. Dellborg. 2016. "Survivorship in Children and Young Adults with Congenital Heart Disease in Sweden." *JAMA Intern Med*.
- Mitchell, S. C., S. B. Korones, and H. W. Berendes. 1971. "Congenital heart disease in 56,109 births. Incidence and natural history." *Circulation* 43 (3):323-32.
- Moore, J. P., B. Mondesert, M. S. Lloyd, S. C. Cook, A. N. Zaidi, R. H. Pass, A. S. John, F. A. Fish, K. M. Shannon, J. A. Aboulhosn, P. Khairy, and Cardiology Alliance for Adult Research in Congenital. 2016. "Clinical Experience With the Subcutaneous Implantable Cardioverter-Defibrillator in Adults With Congenital Heart Disease." *Circ Arrhythm Electrophysiol* 9 (9).
- Murphy, J. G., B. J. Gersh, D. D. Mair, V. Fuster, M. D. McGoon, D. M. Ilstrup, D. C. McGoon, J. W. Kirklin, and G. K. Danielson. 1993. "Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot." *N Engl J Med* 329 (9):593-9.
- Nollert, G., T. Fischlein, S. Bouterwek, C. Bohmer, W. Klinner, and B. Reichart. 1997. "Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair." *J Am Coll Cardiol* 30 (5):1374-83.
- Norgaard, M. A., P. Lauridsen, M. Helvind, and G. Pettersson. 1999. "Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot." *Eur J Cardiothorac Surg* 16 (2):125-30.
- Oechslin, E. N., D. A. Harrison, M. S. Connelly, G. D. Webb, and S. C. Siu. 2000. "Mode of death in adults with congenital heart disease." *Am J Cardiol* 86 (10):1111-6.
- Pundi, K. N., K. N. Pundi, J. N. Johnson, J. A. Dearani, Z. Li, D. J. Driscoll, P. L. Wackel, C. J. McLeod, F. Cetta, and B. C. Cannon. 2016. "Sudden cardiac death and late arrhythmias after the Fontan operation." *Congenit Heart Dis*.
- Raissadati, A., H. Nieminen, J. Haukka, H. Sairanen, and E. Jokinen. 2016. "Late Causes of Death After Pediatric Cardiac Surgery: A 60-Year Population-Based Study." *J Am Coll Cardiol* 68 (5):487-98.
- Ramdjan, T. T., A. Yaksh, J. W. Roos-Hesselink, and N. M. de Groot. 2015. "Endovascular catheter ablation of ventricular tachycardia in a patient with a surgically repaired congenital left ventricular aneurysm." *Neth Heart J* 23 (7-8):370-2.
- Reid, G. J., G. D. Webb, M. Barzel, B. W. McCrindle, M. J. Irvine, and S. C. Siu. 2006. "Estimates of life expectancy by adolescents and young adults with congenital heart disease." *J Am Coll Cardiol* 48 (2):349-55.
- Santharam, S., L. Hudsmith, S. Thorne, P. Clift, H. Marshall, and J. De Bono. 2016. "Long-term follow-up of implantable cardioverter-defibrillators in adult congenital heart disease patients: indications and outcomes." *Europace*.

- Silka, M. J., B. G. Hardy, V. D. Menashe, and C. D. Morris. 1998. "A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects." *J Am Coll Cardiol* 32 (1):245-51.
- Stamm, C., I. Friehs, J. E. Mayer, Jr., D. Zurakowski, J. K. Triedman, A. M. Moran, E. P. Walsh, J. E. Lock, R. A. Jonas, and P. J. Del Nido. 2001. "Long-term results of the lateral tunnel Fontan operation." *J Thorac Cardiovasc Surg* 121 (1):28-41.
- Teuwen, C. P., T. T. Ramdjan, M. Gotte, B. J. Brundel, R. Evertz, J. W. Vriend, S. G. Molhoek, H. G. Dorman, J. M. van Opstal, T. C. Konings, P. van der Voort, E. Delacretaz, C. Houck, A. Yaksh, L. J. Jansz, M. Witsenburg, J. W. Roos-Hesselink, J. K. Triedman, A. J. Bogers, and N. M. de Groot. 2015. "Time Course of Atrial Fibrillation in Patients with Congenital Heart Defects." *Circ Arrhythm Electrophysiol* 8 (5):1065-72.
- Teuwen, C. P., T. T. Ramdjan, M. Gotte, B. J. Brundel, R. Evertz, J. W. Vriend, S. G. Molhoek, H. G. Reinhart Dorman, J. M. van Opstal, T. C. Konings, P. van der Voort, E. Delacretaz, N. J. Wolfhagen, V. van Gastel, P. de Klerk, D. A. Theuns, M. Witsenburg, J. W. Roos-Hesselink, J. K. Triedman, A. J. Bogers, and N. M. de Groot. 2016. "Non-sustained ventricular tachycardia in patients with congenital heart disease: An important sign?" *Int J Cardiol* 206:158-63.
- Teuwen, C. P., Y. J. Taverne, C. Houck, M. Gotte, B. J. Brundel, R. Evertz, M. Witsenburg, J. W. Roos-Hesselink, A. J. Bogers, N. M. de Groot, and Danara Study Investigators. 2016. "Tachyarrhythmia in patients with congenital heart disease: inevitable destiny?" *Neth Heart J* 24 (3):161-70.
- Triedman, J. K. 2002. "Arrhythmias in adults with congenital heart disease." *Heart* 87 (4):383-9.
- Van der Linde, D., E. E. Konings, M. A. Slager, M. Witsenburg, W. A. Helbing, J. J. Takkenberg, and J. W. Roos-Hesselink. 2011. "Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis." *J Am Coll Cardiol* 58 (21):2241-7.
- Vogels, R. J., C. P. Teuwen, T. T. Ramdjan, R. Evertz, P. Knops, M. Witsenburg, J. W. Roos-Hesselink, A. J. Bogers, and N. M. de Groot. 2017. "Usefulness of Fragmented QRS Complexes in Patients With Congenital Heart Disease to Predict Ventricular Tachyarrhythmias." *Am J Cardiol* 119 (1):126-31.
- Weindling, S. N., J. P. Saul, W. J. Gamble, J. E. Mayer, D. Wessel, and E. P. Walsh. 1998. "Duration of complete atrioventricular block after congenital heart disease surgery." *Am J Cardiol* 82 (4):525-7.
- Westhoff-Bleck, M., J. Briest, D. Fraccarollo, D. Hilfiker-Kleiner, L. Winter, U. Maske, M. A. Busch, S. Bleich, J. Bauersachs, and K. G. Kahl. 2016. "Mental disorders in adults with congenital heart disease: Unmet needs and impact on quality of life." *J Affect Disord* 204:180-6.

- Wolff, G. S., T. W. Rowland, and R. C. Ellison. 1972. "Surgically induced right bundle-branch block with left anterior hemiblock. An ominous sign in postoperative tetralogy of Fallot." *Circulation* 46 (3):587-94.
- Yap, S. C., J. W. Roos-Hesselink, E. S. Hoendermis, W. Budts, H. W. Vliegen, B. J. Mulder, A. P. van Dijk, M. J. Schalij, and W. Drenthen. 2007. "Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study." *Eur Heart J* 28 (15):1854-61.
- Zomer, A. C., C. S. Uiterwaal, E. T. van der Velde, J. G. Tijssen, E. C. Mariman, C. L. Verheugt, I. Vaartjes, P. G. Pieper, F. J. Meijboom, D. E. Grobbee, and B. J. Mulder. 2011. "Mortality in adult congenital heart disease: are national registries reliable for cause of death?" *Int J Cardiol* 152 (2):212-7.

Chapter 6

SUDDEN CARDIAC DEATH IN WOMEN

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ABSTRACT

Women have a lower incidence of sudden coronary death as compared to men. In two thirds of women who died suddenly, sudden cardiac death was the first clinical manifestation of coronary heart disease. Post menopausal women have the greatest population burden of cardiovascular disease including SCD. The etiology of SCD in women is less clear, because women are underrepresented in studies of SCD and experience fewer SCD events than men. Several studies suggest that pre-existing coronary disease is less predictive in women, and other etiologies are more likely. Also, women with SCD are less likely to have underlying coronary artery disease (CAD) than men that makes necessary to identify risk factors other than CAD or systolic dysfunction. Heart failure with preserved left ventricular systolic function, increased sympathetic excitability which may be assessed by meta-iodobenzylguanidine uptake, depression, and/or use of antidepressants are common risk factors of SCD in women. Prediction and prevention of SCD is an area of active investigation but current guidelines for preventive intervention are applicable to a very small portion of the population at risk. Only small percentages of women were involved into the studies upon which the guidelines were constructed.

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INTRODUCTION

Sudden cardiac death (SCD) is a major public health problem because of its frequency and demographics. Approximately 50% of all SCDs are unexpected first expressions of a cardiac disorder. Although coronary heart disease (CHD) underlies most SCD events, SCD is the first manifestation of CHD for the majority of victims, particularly among women. Death rates in women with coronary disease were one-fourth that in men with coronary artery disease (Mann, Zipes, et al. 2015, Stecker, Vickers, et al. 2006, Albert, Chae, et al. 2003). Substantial reductions in SCD incidence require effective primary preventive intervention. Mortality from heart disease has actually increased in younger women (<45 years) since 2001. Studies showed that after experiencing myocardial infarction, women and men have a 4- to 10-fold higher risk of SCD, respectively (Mann, Zipes, et al. 2015, Deo, Albert, et al. 2012). It was also observed that women were somewhat more likely to have unrecognized myocardial infarction than men. Women are 28% more likely than men to die within the first year after an infarction. The outcomes of cardiovascular diseases (CVD) changes due to differences in specific CVD risk factors in women, treatment and management strategies for both primary and secondary prevention of CVD, and also pathophysiologic differences in CVD. Studies about genetic markers predictive of CVD had not given additional information about risk assessment of women beyond traditional risk factors (Mann, Zipes, et al., 2015, Go et al., 2014).

EPIDEMIOLOGY

Incidence of SCD is difficult to estimate since numbers vary as a function of the prevalence of coronary heart disease in different countries. SCD is responsible for over half of cardiovascular deaths, 15-20% of total deaths each year and is the first manifestation of heart disease for a large proportion of victims, especially among women. In the United States (US), CVD caused 455,000 women death in 2005. In recent prospective studies, using multiple sources in the US, Netherlands, Ireland and China, SCD rates range from 50 to 100 per 100000 in the general population. Despite the need for multiple sources of surveillance to provide a more accurate estimate of SCD incidence, it is clear that the overall burden in the population remains high (Albert, Chae, et al. 2003, Deo, Albert, et al. 2012). The incidence of SCD increases with age regardless of sex or race. However the incidence of SCD in women lagged behind that in men by approximately 20 years. At any age, women have a lower incidence of SCD than men, even after adjustment for CHD risk factors. This discrepancy may be decreasing over time. However in a study about postmenopausal women incidence rate of SCD found to

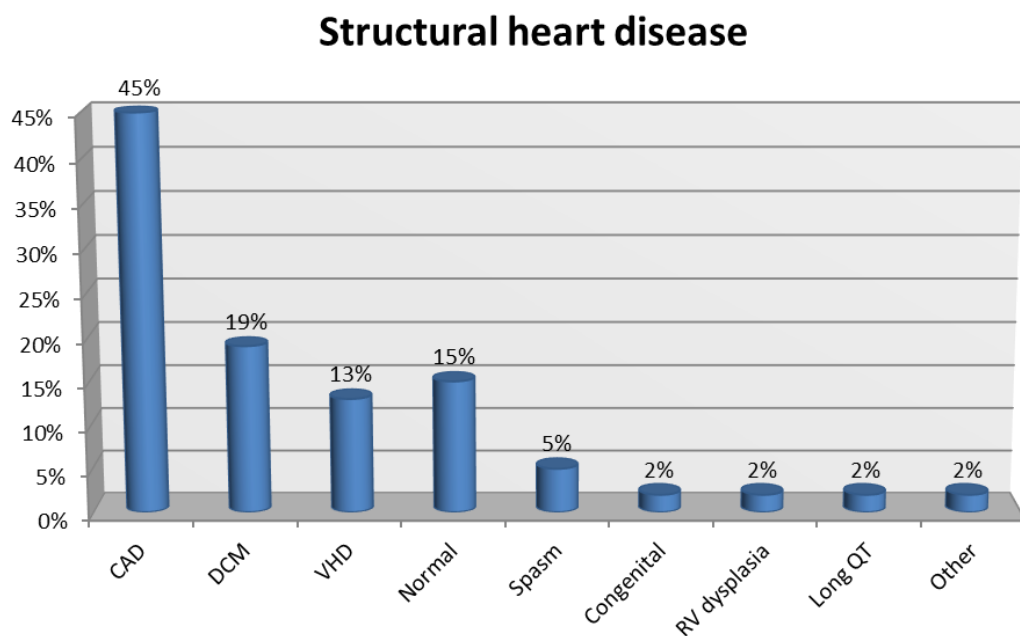
be lower than previously estimated (Bertoia, 2012). Two-thirds of women who present with SCD have no known history of heart disease compared with 50% of men. In addition, among cardiac arrest survivors and SCD patients, women appear to have a higher prevalence of structurally normal heart (Deo, Albert, et al. 2012, Chugh, 2009, Kannel, 1998). There are also racial differences in the incidence of SCD that are not well understood. Black men and women appear to experience out-of-hospital cardiac arrest several years earlier than whites (Becker, 1993).

Sex differences in cardiac electrophysiology that have important clinical and therapeutic implications also affect the epidemiology, presentation and prognosis of various arrhythmia and sudden cardiac death. The potential mechanisms include differences in cardiac size, structure, and the different ways in which hormones, drugs, and electrolytes affect cardiac ion channels in men and women (Curtis, 2012). Women have higher resting heart rates starting at puberty than men. They also have longer QT intervals and a greater risk for drug induced torsades des pointes (Makkar, 1993). Atrioventricular (AV) nodal reentrant tachycardia is twice as common in women as in men. However AV reentrant tachycardia and Wolff-Parkinson-White syndrome are more common in men. Women with atrial fibrillation have a higher risk for stroke and are less likely to receive anticoagulation and ablation procedures (Mann, Zipes, 2015, Albert, McGovern, et al. 1996). A prospective population-based study for out of-hospital cardiac arrest found that women more often presented with asystole and pulseless electrical activity, and men usually had ventricular tachycardia and ventricular fibrillation (Wigginton, 2002). Also, women, especially at younger ages seem to have a higher rate of successful resuscitation and survival from shockable rhythms, possibly because of favorable effects of smaller body size and estrogen on success of defibrillation and postresuscitation hemodynamics (Myerburg, 2004).

PATHOPHYSIOLOGY

Coronary heart disease is the most common substrate underlying SCD in the Western world, being responsible for 75% of SCDs. Acute myocardial infarction, ischemia without infarction, and structural alterations such as scar formation or ventricular dilatation secondary to prior infarction or chronic ischemia may be the predisposing causes of SCD in CHD. In 5% of SCDs or cardiac arrests, a significant cardiac abnormality is not found after extensive evaluation or at autopsy (Priori, 1992, Chugh, 2000, Cupples, 1992). The Framingham study found that overt coronary artery disease before death markedly elevated the risk of SCD in both genders, although the death rates in women with coronary disease were one-fourth that in men with coronary artery disease (Kannel, 1998). Cardiac failure increased the risk of SCD 5-fold in both sexes, although the absolute risk of SCD in women was one-third of that in men (Curtis, 2012). In a

retrospective analysis of 355 survivors (271 men, 84 women) of out-of-hospital cardiac arrest survivors in Boston, mentioned that a left ventricular ejection fraction (LVEF) <40%, which was the strongest independent predictor of total and cardiac mortality in men, did not have the same prognostic significance in women. This study suggests that studies analyzing especially women population should be conducted instead of generalizing data from predominantly male population (12). Proportions of underlying cardiac disease among women who survive out-of-hospital cardiac arrests are given in Figure 1 (Albert, McGovern, et al. 1996).



CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; VHD, valvular heart disease; SPASM, coronary vasospasm; and RV, right ventricular (Albert, McGovern, et al. 1996).

Figure 1. Structural heart disease in cardiac arrest survivors. This graphic depict the proportions of underlying cardiac disease among women who survive out-of-hospital cardiac arrests. The mean age was 55 ± 17 years.

RISK FACTORS

Modifiable CHD risk factors that have been demonstrated to predict SCD in diverse cohorts include hypertension, hypercholesterolemia, diabetes mellitus, kidney dysfunction, obesity and smoking. Family history of premature CVD in first-degree relatives, before 55 years of age in men and 65 years of age in women, increases the risk of CVD (Mann, Zipes, 2015, Deo, Albert, et al. 2012). Conventional risk factors still appear to predict SCD in women. In a cohort with a follow up of more than 20 years, at least one of the CHD risk factors had been reported by 94% and at least 2 risk factors had

been reported by 73% in women who died suddenly. Smoking, diabetes and hypertension showed the strongest relations with SCD. Heavy smoking and parental history of myocardial infarction (MI) were also found to be important risk factors especially for women younger than 60 years (Albert, Chae, et al. 2003). Conflicting data has also showed that with the exception of diabetes, kidney disease and smoking other risk factors do not appear to predict SCD risk once overt CHD has been established (Kannel, 1998, Cupples, 1992). Besides traditional risk factors for coronary heart disease, risk factors for sudden cardiac death in postmenopausal women include black race, higher pulse, higher waist-to-hip ratio, elevated white blood cell count, and heart failure (Bertoia, 2012). Deo et al. reported that myocardial infarction, heart failure, eGFR <40 ml/min/1.73 m², atrial fibrillation, physical inactivity and diabetes improved SCD prediction when used in addition to LVEF (Deo et al., 2011). In another study including 81,722 US women, from Nurses' Health Study were examined. A low-risk lifestyle was defined as not smoking, BMI <25 kg/m², exercise ≥ 30 minutes/day, and top 40% of the Alternate Mediterranean Diet Score, which emphasizes high intake of vegetables, fruits, nuts, legumes, whole grains, fish and moderate intake of alcohol. The absolute risks of SCD were 22, 17, 18, 13 and 16 cases/100,000 person-years among women with 0, 1, 2, 3 and 4 low risk factors, respectively. They concluded that adherence to a low-risk lifestyle was associated with a low risk of SCD and may be an effective strategy for the prevention of SCD in the general population (Chiuve, 2011).

Also, compared with current smokers, in women without coronary heart disease the risk of SCD was significantly lower within 5 years of quitting smoking (multivariable hazard ratio: 0.47; 95% confidence interval: 0.24-0.92), and the risk of SCD resembled that of never smokers after 20 years of abstinence (Kannel, 1998, Cupples, 1992, Al-Khatib, 2016). Systematic CV risk assessment is recommended as class of recommendation Class IIB, with a level of evidence C (data derived from a single randomized clinical trial or large non-randomized studies) in women >50 years of age or post-menopausal with no known CV risk factors. Additionally, although there are no data to support the beneficial effects screening for CV risk factors in women before prescribing combined oral contraception, screening specific groups with jobs that place other people at risk, e.g., bus drivers and pilots, may be reasonable. Premature menopause, better defined as primary ovarian insufficiency, occurs in roughly 1% in women ≤ 40 years of age. It has been reported to be associated with an increased risk of CVD (Piepoli et al., 2016).

Diet and Exercise Factors

In the Nurses' Health Study, the relative risk of SCD was significantly lower among women in the highest quartile of dietary magnesium intake. Recent data from the Nurses'

Health Study suggest that women whose dietary habits most resemble the Mediterranean dietary pattern have a significantly lower risk of SCD (Zarraga, 2006, Chiuve, 2011). Despite the long-term benefits of exercise, it is also well known that SCD occurs with a higher-than-average frequency during or shortly after vigorous exertion. The magnitude of the risk associated with exertion appears to be lower among women where exertion-related SCD is much less common (Kohl, 1992, Marijon, 2011).

Psychosocial Risk Factors

Population based studies showed that chronic psychological stressors such as anxiety disorders and depression have also been associated with SCD. Phobic anxiety has been directly associated with SCD, but not nonfatal MI risk, in 3 separate populations of men and women. Depression has also been associated with elevated risks of cardiac arrest and SCD among women without CHD (Whang et al., 2009). Also, the INTERHEART study has shown that a cluster of psychosocial risk factors (i.e., social deprivation, stress at work or in family life and depression) is associated with increased risk for myocardial infarction (MI) (RR 3.5 for women and 2.3 for men). The population attributable risk was 40% in women and 25% in men (Piepoli et al., 2016).

Genetic Factors

Genetic variants that are associated with CHD may also serve as susceptibility alleles for SCD in the general population. In 60 women with SCD, 6 rare missense variants (10%) were identified in the cardiac sodium channel gene (SCN5A). The overall frequency of these rare variants in SCN5A was significantly higher in the SCD cases than in 733 controls from the same population and subtle alterations in ion channel function were observed for 4 of the 5 variants. Although not a common cause of SCD, data suggest that functionally significant mutations and rare variants in SCN5A may contribute to SCD risk among women in whom the prevalence of structural heart disease is lower (Deo, Albert, et al. 2012, Albert, McGovern, et al. 1996, Albert et al., 2008). The majority of mitral valve prolapse is thought to be benign, but there are certain characteristics such as leaflet thickness, redundancy, and increased LV diameter that seem to be associated with higher risk, and recent data suggest that women with bileaflet prolapse and complex ventricular ectopy may be at particular risk. Overall, data on SCD risk stratification and appropriate use of ICDs in patients with valvular disease are scarce and further studies in this at risk subgroup of patients are needed (Hayashi et al., 2015).

Table 1. Gender Outcomes in Implantable Cardioverter Defibrillator Clinical Trials (10)

Enrollment		
Trial	% included female	End Points with outcome hazard ratios
AVID	21	Mortality rate in women 14.4%
MADIT I	8	Mortality is not stratified by gender
MADIT II	16	Mortality was the end point Outcomes with therapy in women: 0,57 (p:0.132), men: 0,66 (p:0.011)
MUSTT	10	Outcome hazard ratio results with EP- guided therapy in arrhythmic death and cardiac arrest patients found no difference between men and women
SCD-HcFT	23	Mortality was the end point Outcomes in women:0.96 (0.58-1.61)
DEFINITE	29	Mortality was the end point women: >1.0

Abbreviations: AVID, Antiarrhythmics Versus Implantable Defibrillators; CI, confidence interval; DEFINITE, Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation; EP, electrophysiological; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

MANAGEMENT AND TREATMENT STRATEGIES

Gender differences also affect management and treatment strategies in women. Implantable cardioverter defibrillators (ICDs) have been shown to decrease mortality when used for both primary and secondary prevention of SCD (Curtis, 2012). The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial examined the use of ICDs for the secondary prevention of SCD. Despite gender differences in baseline characteristics and clinical arrhythmia at the time of presentation mortality was similar in women (14.4%) and men (15.5%) who received an ICD, as compared to 24.4% in the control group (AVID Investigators, 1997). The Multicenter Unsustained Tachycardia Trial (MUSTT) showed the mortality reduction by therapy guided by electrophysiologic testing in patients with coronary disease, ejection fraction $\leq 40\%$. Women were only 14% of all study population. In a post-hoc analysis of patients enrolled in MUSTT, gender difference did not influence benefit of EP-guided therapy (Buxton, 1999, Russo et al. 2004). The Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) investigated the use of ICDs for primary prevention of SCD in patients with heart failure and ejection fraction

$\leq 35\%$ compared to amiodarone therapy or placebo without further risk stratification. There was a statistically significant decrease in mortality rates in men but not in women (Bardy, 2005). The smaller number of women enrolled in these clinical trials, may explain why treatment effects are different among women and more difficult to detect. Data from a sample of Medicare beneficiaries who met the criteria ICD implantation for the primary prevention of SCD revealed that only 8.6/1000 women received an ICD compared with 32.3/1000 men within 1 year of diagnosis (Ghanbari et al., 2009). Gender outcomes in ICD clinical trials are given in Table 1.

An observational study of more than 13000 patients admitted with systolic heart failure (LVEF < 30%) to hospitals participating in the American Heart Association's Get With the Guidelines - HeartFailure program showed that after adjustment for patient characteristics and hospital factors, the adjusted odds of ICD use were 0.73 for black men, 0.62 for Caucasian women, and 0.56 for black women, compared with Caucasian men (Hernandez et al. 2007).

CRT Treatment

Cardiac resynchronization therapy (CRT) improves symptoms and outcomes in patients with systolic heart failure and ventricular dyssynchrony. Results from multiple clinical trials have found CRT to be as effective, if not more so, in women as compared to men (Curtis, 2006). In a subgroup analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, women who received CRT therapy experienced statistically significant improvements in time to first heart failure hospitalization and death compared to women not treated with CRT (Woo et al., 2005). Table 2 shows gender outcomes in CRT clinical trials (Curtis, 2006).

The greater prevalence of ischemic cardiomyopathy in men (scar can not be responsive to pacing) may explain the low degree of benefit from therapy. These gender differences persist even when controlling for etiology of heart failure (Curtis et al. 2012). An observational registry by Lilli et al. revealed that female gender was independently associated with a better response to CRT, defined as the degree of left ventricular reverse remodeling as assessed by echocardiographic reduction of left ventricular end-systolic volume. The randomized trials and observational studies are consistent with the low incidence of ICD implantation in women patients for primary prevention. The common question is whether this situation is due to referral bias or refusal bias. Individual-patient data analysis of 3 large randomized CRT-D trials enrolling primarily patients with NYHA class II heart failure is that women with LBBB by conventional ECG criteria derive significant benefit from CRT-D at QRS durations shorter than 150 milliseconds (specifically, ≥ 130 milliseconds), while men with conventional LBBB derive significant benefit at QRS of 150 milliseconds or longer (Zusterzeel et al., 2014). This analysis

found that women with LBBB and QRS of 130 to 149 milliseconds have a 76% reduction in heart failure events and mortality from CRT-D. Another fact that women normally have smaller ventricles and shorter QRS duration than men provides an anatomical and/or physiological explanation for the findings (Zusterzeel et al., 2014).

Table 2. Gender outcomes in CRT clinical trials

CRT trials	Enrollment (% female)	Results
MIRACLE	32%	Women had lower risk of death or HF hospitalization, Clinical endpoints was - NYHA, 6MHWD, QOL
Path-CHF	48%	Endpoint: peak O ₂ consumption, 6MHWD Outcome hazard ratio: Not stratified by gender,
MUSTIC	25%	Endpoint: 6MHWD Outcome hazard ratio: Not stratified by gender
COMPANION	33%	Endpoint: Mortality or hospitalization for any cause No significant difference in hazard ratio
CARE-HF	26%	Endpoint: Mortality or unplanned hospitalization for major CV event Outcome hazard ratio in women: 0.64 (0.42-0.97)

MIRACLE: Multi-center InSync Randomized Clinical Evaluation, Path-CHF: Pacing Therapy for Congestive Heart Failure, MUSTIC: Multisite Stimulation in Cardiomyopathy, COMPANION: Comparison of Medical Therapy, Pacing and Defibrillation, CARE-HF: Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure, CV: Cardiovascular, 6MHWD: 6 minute hall wall distance, NYHA: New York Heart Association, QOL: quality of life.

Age may affect selection of physicians for patients to ICD implantation. Indeed, the women were older in many trials (Russo et al., 2004, Curtis et al., 2007). The age difference may affect the implantations, due to initial referral bias or older patients may be less willing for ICD therapy (Davis et al., 2006). However, the survival benefit from ICD therapy was shown to be comparable with younger patients (Duray et al., 2005). According to a retrospective analysis, gender difference was most marked in patients ≥ 80 years. In this age group the male to female ratio is 29 (Lin et al., 2008). However this is not the only explanation. In the Canadian registry, women still have low implantation rate, despite their younger age than male patient population (57 vs 64, respectively, $p = 0.01$) and the ages of women and men were similar in MADIT II (Davis et al., 2006, Moss et al., 2002).

Women appeared to have higher probability of out-of-hospital cardiac deaths than men. This might also mislead to underestimation of SCD in women and lead to take less preventive measures (Zheng et al., 2001). Interestingly enough women may refuse ICD

implantation more often (Wolbrette et al., 2002). In a study examining the preferences of support and education of ICD patients, there was significant difference in preferences between genders. Women preferred a support group, interaction with device nurse and professional counselor more than men (Serber et al., 2009). This may be also important for the acceptance of ICD implantation by women. Women may seek for more communication with health team and need more information. Moreover among the ICD recipients, women seem to have poorer psychological adjustment after ICD implantation. Particularly for young women, shock anxiety, death anxiety and body image issues are found to be important causes of distress (Bostwick et al., 2007, Vazquez et al. 2008).

CONCLUSION

Prediction and prevention of SCD is an area of active investigation, but current guidelines for preventive intervention are applicable to only a very small portion of the population at risk, and only small percentages of women were involved in the studies upon which the guidelines were constructed. SCD in women is more predictable with risk factors than estimated and accepted. Risk factor modification and attempts for earlier recognition of cardiovascular diseases in women, with more primary prevention devices and secondary prevention procedures will reduce SCD. In order to protect, prevent and treat both genders we must conduct more trails to provide evidence-based management strategies.

REFERENCES

- Albert, C.M., C.U Chae, F. Grodstein, L.M. Rose, K.M. Rexrode, J.N. Ruskin, M.J. Stampfer, and J.E. Manson. 2003. "Prospective study of sudden cardiac death among women in the United States." *Circulation* 107(16):2096-101.
- Albert, C.M., B.A. McGovern, J.B. Newell, and J.N. Ruskin. 1996. "Sex differences in cardiac arrest survivors." *Circulation* 93:1170-6.
- Albert, C.M., E.G. Nam, E.B. Rimm, H.W. Jin, R.J. Hajjar, D.J. Hunter, C.A. MacRae, and P.T. Ellinor. 2008. "Cardiac sodium channel gene variants and sudden cardiac death in women." *Circulation* 117:16-23.
- Al-Khatib, S.M., C.W. Yancy, P. Solis, L. Becker, E.J. Benjamin, R.G. Carrillo, J.A. Ezekowitz, G.C.Fonarow, B.K. Kantharia, M. Kleinman, G. Nichol, and P.D. Varosy. 2016. "2016 AHA/ACC Clinical Performance and Quality Measures for Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures."

- Circulation: Cardiovascular Quality and Outcomes.* doi: 10.1161/hcq.0000000000000022.
- Bardy, G.H., K.L. Lee, D.B. Mark, J.E. Poole, D.L. Packer, R. Boineau, M. Domanski, C. Troutman, J. Anderson, G. Johnson, S.E. McNulty, N. Clapp-Channing, L.D. Davidson-Ray, E.S. Fraulo, D.P. Fishbein, R.M. Luceri, and J.H. Ip. 2005. "Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure." *N. Engl. J. Med.* 352:225-37.
- Becker, L.B., B.H. Han, P.M. Meyer, F.A. Wright, K.V. Rhodes, D.W. Smith, and J. Barrett. 1993. "Racial differences in the incidence of cardiac arrest and subsequent survival. The CPR Chicago Project." *N. Engl. J. Med.* 329:600-6.
- Bertoia, M.L., M.A. Allison, J.E. Manson, M.S. Freiberg, L.H. Kuller, A.J. Solomon, M.C. Limacher, K.C. Johnson, J.D. Curb, S. Wassertheil-Smoller, and C.B. Eaton. 2012. "Risk factors for sudden cardiac death in post-menopausal women." *JACC* 60(25): 2674-82.
- Bostwick, J.M., and C.L. Sola. 2007. "An updated review of implantable cardiover/defibrillators, induced anxiety, and quality of life." *Psychiatr. Clin. North Am.* 30:677-88.
- Buxton, A.E., K.L. Lee, J.D. Fisher, M.E. Josephson, E.N. Prystowsky, and G. Hafley. 1999. "A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators." *N. Engl. J. Med.* 341:1882-90.
- Chiuve, S.E., T.T. Fung, K.M. Rexrode, D. Spiegelman, J.E. Manson, M.J. Stampfer, and C.M. Albert. 2011. "Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women." *JAMA* 306(1):62-9. doi:10.1001/jama.2011.907.
- Chiuve, S.E., E.C. Korngold, J.L. Jr Januzzi, M.L. Gantzer, and C.M. Albert. 2011. "Plasma and dietary magnesium and risk of sudden cardiac death in women." *Am. J. Clin. Nutr.* 93:253-26.
- Chugh, S.S., K.L. Kelly, and J.L. Titus. 2000. "Sudden cardiac death with apparently normal heart." *Circulation* 102:649-54.
- Chugh, S.S., A. Uy-Evanado, C. Teodorescu, K. Reinier, R. Mariani, K. Gunson, and J. Jui. 2009. "Women have a lower prevalence of structural heart disease as a precursor to sudden cardiac arrest: the ORE-SUDS (Oregon Sudden Unexpected Death Study)." *J. Am. Coll. Cardiol.* 54: 2006-11.
- Cupples, L.A., D.R. Gagnon, and W.B. Kannel. 1992. "Long- and short-term risk of sudden coronary death." *Circulation* 85:111-8.
- Curtis, A.B. 2006. "Are women worldwide under-treated with regard to cardiac resynchronization and sudden death prevention?" *J. Interv. Card. Electrophysiol.* 17:169-75.
- Curtis, A.B., and D. Narasimha. 2012. "Arrhythmias in women." *Clin. Cardiol.* 35(3):166-71.

- Curtis, L.H., S.M. Al-Khatib, A.M. Shea, B.G. Hammill, A.F. Hernandez, and K.A. Schulman. 2007. "Sex differences in the use of implantable cardioverter-defibrillators for primary and secondary prevention of sudden cardiac death." *JAMA* 298(13):1517-24.
- Davis, D.R., A.S.L. Tang, R. Lemery, M.S. Green, M.H. Gollob, and D.H. Birnie. 2006. "Influence of gender on ICD implantation for primary and secondary prevention of sudden cardiac death." *Europace* 8:1054-6.
- Deo, R., and C.M. Albert. 2012. "Epidemiology and Genetics of Sudden Cardiac Death." *Circulation* 125: 620-37.
- Deo, R., E. Vittinghoff, F. Lin, Z.H. Tseng, S.B. Hulley, and M.G. Shlipak. 2011. "Risk factor and prediction modeling for sudden cardiac death in women with coronary artery disease." *Arch. Intern. Med.* 171:1703-9.
- Duray, G., S. Richter, J. Manegold, C.W. Israel, G. Grönefeld, and S.H. Hohnloser. 2005. "Efficacy and safety of ICD therapy in a population of elderly patients treated with optimal background medication." *J. Interv. Card. Electrophysiol.* 14:169-73.
- Ghanbari, H., G. Dalloul, R. Hasan, M. Daccarett, S. Saba, S. David, and C. Machado. 2009. "Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: a metaanalysis of randomized controlled trials." *Arch. Intern. Med.* 169:1500-6.
- Go, A.S., D. Mozaffarian, V.L. Roger, E.J. Benjamin, J.D. Berry, M.J. Blaha, S. Dai, E.S. Ford, C.S. Fox, S. Franco, H.J. Fullerton, C. Gillespie, S.M. Hailpern, J.A. Heit, V.J. Howard, M.D. Huffman, S.E. Judd, B.M. Kissela, S.J. Kittner, D.T. Lackland, J.H. Lichtman, L.D. Lisabeth, R.H. Mackey, D.J. Magid, G.M. Marcus, A. Marelli, D.B. Matchar, D.K. McGuire, E.R. 3rd Mohler, C.S. Moy, M.E. Mussolino, R.W. Neumar, G. Nichol, D.K. Pandey, N.P. Paynter, M.J. Reeves, P.D. Sorlie, J. Stein, A. Towfighi, T.N. Turan, S.S. Virani, N.D. Wong, D. Woo, and M.B. Turner: on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. 2014. "Heart disease and stroke statistics - 2014 update: A report from the American Heart Association." *Circulation* 129:28-292.
- Hayashi, M., W. Shimizu, and C.M. Albert. 2015. "The Spectrum of Epidemiology Underlying Sudden Cardiac Death." *Circulation Research* 116:1887-906.
- Hernandez, A.F., G.C. Fonarow, L. Liang, S.M. Al-Khatib, L.H. Curtis, K.A. LaBresh, C.W. Yancy, N.M. Albert, and E.D. Peterson. 2007. "Sex and racial differences in the use of implantable cardioverter-defibrillators among patients hospitalized with heart failure." *JAMA* 298:1525-32.
- Kannel, W.B., P.W. Wilson, R.B. D'Agostino, and J. Cobb. 1998. "Sudden coronary death in women." *Am. Heart J.* 136:205-12.
- Kohl, H.W. III, K.E. Powell, N.F. Gordon, S.N. Blair, and R.S. Jr Paffenbarger. 1992. "Physical activity, physical fitness, and sudden cardiac death." *Epidemiol. Rev.* 14:37-58.

- Lilli, A., G. Ricciardi, M.C. Porciani, A.P. Perini, P. Pieragnoli, N. Musilli, A. Colella, S. Del Pace, A. Michelucci, F. Turreni, M. Sassara, A. Achilli, S.S. Barold, and L. Padeletti. 2007. "Cardiac resynchronization therapy: gender related differences in left ventricular reverse remodeling." *Pacing Clin. Electrophysiol.* 30:1349-55.
- Lin, G., R.A. Meverden, D.O. Hodge, D.Z. Uslan, D.L. Hayes, and P.A. Brady. 2008. "Age and gender trends in implantable cardioverter defibrillator utilization: A population based study." *J. Interv. Electrophysiol.* 22:65-70.
- Makkar, R.R., B.S. Fromm, R.T. Steinman, M.D. Meissner, and M.H. Lehmann. 1993. "Female gender as a risk factor for torsades de pointes associated with cardiovascular drugs." *JAMA* 270(21):2590-7.
- Mann, D.L., D.P. Zipes, P. Libby, and R.O. Bonow. 2015. *Braunwald's Heart Disease: A textbook of cardiovascular medicine, 10th edition*. Saunders.
- Marijon, E., M. Tafflet, D.S. Celermajer, F. Dumas, M.C. Perier, H. Mustafic, J.F. Toussaint, M. Desnos, M. Rieu, N. Benameur, J.Y. Le Heuzey, J.P. Empana, and X. Jouven. 2011. "Sports-related sudden death in the general population." *Circulation* 124:672-68.
- Moss, A.J., W. Zareba, A.J. Hall, H. Klein, D.J. Wilber, D.S. Cannom, J.P. Daubert, S.L. Higgins, M.W. Brown, and M.L. Andrews. 2002. "Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction." *N. Engl. J. Med.* 346:877-83.
- Myerburg, R.J., A. Interian, J. Simmons et al. 2004. "Sudden cardiac death." In: *Cardiac Electrophysiology: From Cell to Bedside*, edited by Zipes DP, 720-31. Philadelphia, PA: WB Saunders.
- Piepoli, M.F., A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, M.T. Cooney, U. Corrà, B. Cosyns, C. Deaton, I. Graham, M.S. Hall, F.D. Hobbs, M.L. Løchen, H. Löllgen, P. Marques-Vidal, J. Perk, E. Prescott, J. Redon, D.J. Richter, N. Sattar, Y. Smulders, M. Tiberi, H.B. van der Worp, I. van Dis, and W.M. Verschuren. 2016. "2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR)." *European Heart Journal* 37(29):2315-81. doi: 10.1093/eurheartj/ehw106.
- Priori, S.G., M. Borggrefe, A.J. Camm, R.N. Hauer, H. Klein, K.H. Kuck, P.J. Schwartz, P. Touboul, and H.J. Wellens. 1992. "Unexplained cardiac arrest. The need for a prospective registry." *Eur. Heart J.* 13:1445-6.
- Russo, A.M., N.J. Stamato, M.H. Lehmann, G.E. Hafley, K.L. Lee, K. Pieper, and A.E. Buxton. 2004. "Influence of gender on arrhythmia characteristics and outcome in the

- Multicenter Unsustained Tachycardia Treatment Trial.” *J. Cardiovasc. Electrophysiol.* 15:993-8.
- Serber, A.R., N.J. Finch, R.B. Leman, L.J. Sturdivant, T. Barnes, E. Clarke, J. Garry, and M.R. Gold. 2009. “Disparities in preferences for receiving support and education among patients with implantable cardioverter defibrillators.” *Pacing Clin. Electrophysiol.* 32:383-90.
- Stecker, E.C., C. Vickers, J. Waltz, C. Socoteanu, B.T. John, R. Mariani, J.H. McAnulty, K. Gunson, J. Jui, and S.S. Chugh. 2006. “Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon sudden unexpected death study.” *J. Am. Coll. Cardiol.* 47(6):1161-6.
- The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. 1997. “A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias.” *N. Engl. J. Med.* 337(22):1576-83.
- Vazquez, L.D., E.A. Kuhl, J.B. Shea, A. Kirkness, J. Lemon, D. Whalley, J.B. Conti, and S.F. Sears. 2008. “Age-specific differences in women with implantable cardioverter defibrillators: An international multi center study.” *Pacing Clin. Electrophysiol.* 31:1528-34.
- Whang, W., L.D. Kubzansky, I. Kawachi, K.M. Rexrode, C.H. Kroenke, R.J. Glynn, H. Garan, and C.M. Albert. 2009. “Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses’ Health Study.” *J. Am. Coll. Cardiol.* 53:950-8.
- Wigginton, J.G., P.E. Pepe, J.P. Bedolla, L.A. DeTamble, and J.M. Atkins. 2002. “Sex-related differences in the presentation and outcome of out-of-hospital cardiopulmonary arrest: a multiyear, prospective, population-based study.” *Crit. Care Med.* 30: 131-6.
- Wolbrette, D., G. Naccarelli, A. Curtis, M. Lehmann, and A. Kadish. 2002. “Gender differences in arrhythmias.” *Clin. Cardiol.* 25:49-56.
- Woo, G.W., S. Petersen-Stejskal, J.W. Johnson, J.B. Conti, J.A. Jr Aranda, and A.B. Curtis. 2005. “Ventricular reverse remodeling and 6-month outcomes in patients receiving cardiac resynchronization therapy: analysis of the MIRACLE Study.” *J. Intervent. Card. Elect.* 12:107-13.
- Zarraga, I.G., and E.R. Schwarz. 2006. “Impact of dietary patterns and interventions on cardiovascular health.” *Circulation* 114:961-73.
- Zheng, Z.J., J.B. Croft, W.H. Giles, and G.A. Mensah. 2001. “Sudden cardiac death in the United States, 1989 to 1998.” *Circulation* 104:2158-63.

Zusterzeel, R., K.A. Selzman, W.E. Sanders, D.A. Caños, K.M. O'Callaghan, J.L. Carpenter, I.L. Piña, and D.G. Strauss. 2014. "Cardiac Resynchronization Therapy in WomenUS Food and Drug Administration Meta-analysis of Patient-Level Data." *JAMA Intern. Med.* 174(8):1340-8. doi:10.1001/jamainternmed.2014.2717.

Chapter 7

NEW ADVANCES IN SUDDEN CARDIAC DEATH (SCD) RISK STRATIFICATION IN HYPERTROPHIC CARDIOMYOPATHY

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ABSTRACT

SCD is the most devastating complication of HCM and it has an annual incidence of 1%. SCD accurate risk estimation can be extremely challenging and it recently became a source of argument between European and American experts. Although the main risk factor of SCD is definitely a previous resuscitated cardiac arrest, the identification of individuals at high risk of SCD in primary prevention is still a debated issue. This is due to the fact that recommendations are based on observational, retrospective cohort studies. Historically, five risk factors were considered at risk for SCD and the presence of 2 or more of these have been considered an indication for ICD implantation for primary prevention, i.e., familiar history of SCD, syncope, maximal left ventricular (LV) wall thickness, non-sustained ventricular tachycardia (NSVT), abnormal blood pressure response to exercise. The 2011 ACCF/AHA guidelines have confirmed this timeworn recommendation assigning a major role to the first three risk factors. On the other side of the Atlantic sea, the most recent (2014) ESC guidelines endorsed a new risk prediction model which includes: age, family history of SCD, unexplained syncope, LV outflow tract obstruction, maximal LV wall thickness, left atrial diameter, NSVT. The EU model was validated after a multicentre, retrospective cohort study of 3675 patients and it's significantly more accurate with respect to the USA model based on old-fashioned and

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little populations of patients. Nonetheless, over the last few years, cardiovascular research is going very fast in discovering new modifying risk factors. Thus, LV apical aneurysm, multiple sarcomere gene mutations, myocardial fibrosis (MF) and End-Stage (ES) HCM are becoming more and more important, especially in cases at intermediate risk. Therefore, a large number of study and two meta-analyses were published on MF, which is showing to be an independent strong risk predictor of cardiovascular mortality and of SCD. In particular, a recent study showed that a LGE extent $\geq 15\%$ of the LV mass confer a >2 -fold risk of SCD and a LGE amount $\geq 20\%$ conveys a >3 -fold increase in risk of ES-HCM evolution.

Finally, an original multicentre European study provided the first detailed quantitative histological evaluation of extent, distribution, patterns and types of MF in a large population of ES-HCM explanted hearts. Moreover, it evaluated quantitative relationship between LGE-CMR assessment and histometric analysis of MF. It explored new perspectives on MF, on its imaging assessment and ultimately on the physiopathology of HCM and of SCD.

Keywords: hypertrophic cardiomyopathy, sudden cardiac death, risk factors, myocardial fibrosis

INTRODUCTION

HCM is defined by the presence of myocardial hypertrophy (i.e., a wall thickness ≥ 15 mm in one or more left ventricular (LV) myocardial segments as measured by any imaging technique -echocardiography, cardiac magnetic resonance imaging (CMR) or computed tomography) in the absence of haemodynamic stresses sufficient to account for the degree of hypertrophy (such as valvular heart diseases, hypertension, congenital heart disease) and systemic diseases such as amyloidosis and glycogen storage disease which can be responsible of increased myocardial thickness (Elliott, 2014., Elliott, 2008.).

In children, the diagnosis of HCM requires an LV wall thickness more than two standard deviations greater than the predicted mean (z-score >2 , where a z-score is defined as the number of standard deviations from the population mean) (Elliott, 2014.).

HCM is the most frequent heritable genetic heart disease, with an estimated prevalence of 1 in 500 people corresponding to 0.2% of the global population. However, the most recent genetic populations studies report a higher prevalence of 1 in 200 people (Semsarian, 2015.).

In more than 60% of adolescents and adults with HCM, the disease is spread by one or more mutations of one or more cardiac sarcomere protein genes (Elliott, 2014.). Moreover, it is important to note that many others cardiac genetic and non-genetic diseases can mimic the sarcomeric HCM phenotype (5-10% of cases). These are the so called “phenocopies of sarcomeric HCM” (Figure 1).

Natural history of HCM is extremely heterogenous. The vast majority of patients are asymptomatic and have a normal expectancy of life (near 70%). Many others develop the

main complications of HCM that are: atrial fibrillation and thromboembolic events, infective endocarditis (in patients with obstructive HCM), SCD, end-stage HCM (ES-HCM) and advanced heart failure.

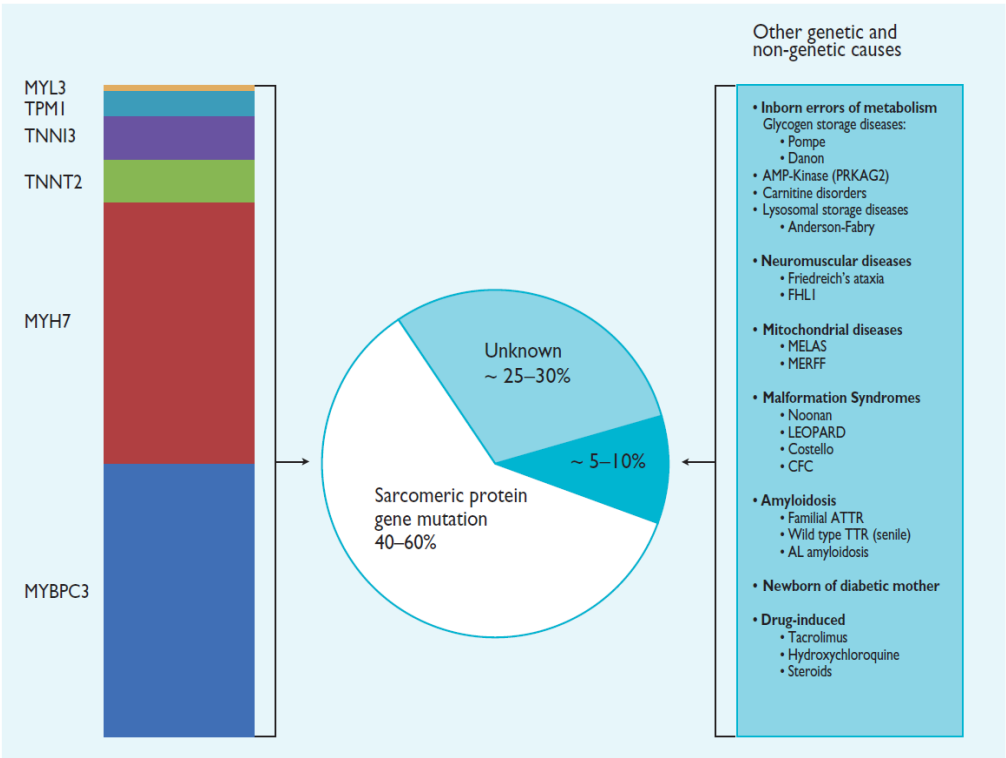


Figure 1. Different aetiologies of HCM (from Elliot PM et al) (Elliott 2014).

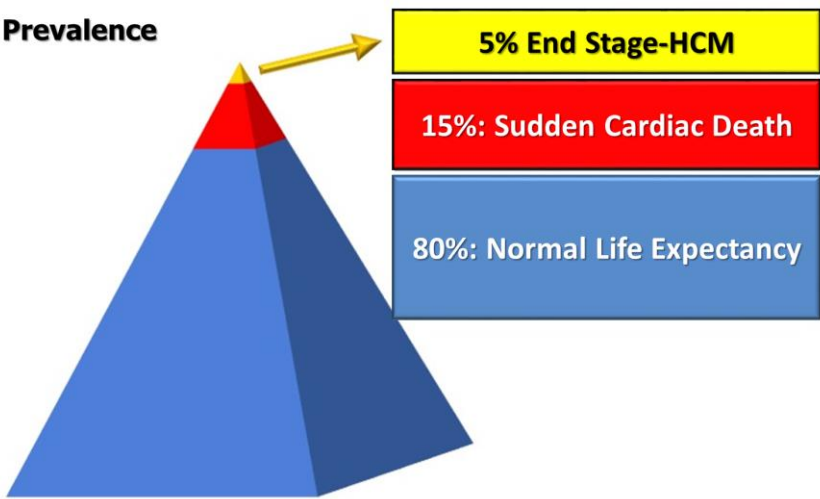


Figure 2. Prevalence of the two most ominous complications in HCM.

Although some recent papers report an annual mortality $<1\%$ using the contemporary therapeutic armamentarium (Implantable cardioverter-defibrillators (ICD), cardiac transplantation and stroke prophylaxis), the rate of life-threatening or disabling events per year still remains high. Indeed, in those cohorts nearly 15% of patients died suddenly or had an appropriate ICD shock or developed progressive heart failure. Additionally, the 19% of patient developed atrial fibrillation or stroke (Elliott, 2016., Maron, 2016.).

Thus, both SCD and End-Stage HCM are the most ominous complications, and we can summarize this concept in Figure 2.

CURRENT STATE-OF-THE-ART SCD RISK STRATIFICATION IN HCM

SCD is defined as a natural death from cardiac causes, occurring unexpectedly within 1 hour of the onset of new symptoms or as a death that was unwitnessed and unexpected, unless a specific noncardiac cause of death has been found. The key elements are: natural, rapid and unexpected.

SCD is the most devastating and awful complication of HCM and the most contemporary studies report an estimated annual incidence of 1% (Elliott, 2014., Gersh, 2011., Weissler-Snir, 2016.).

The main causes of SCD are fatal arrhythmic event such as ventricular fibrillation, polymorphic ventricular tachycardia and pulseless electrical activity.

TABLE 1. ASSESSMENT OF SCD RISK IN HCM PATIENTS

Tool	Clue associated with SCD
Clinical History	<ul style="list-style-type: none"> • Personal positive history for resuscitated cardiac arrest (negative history for coronary artery diseases, valvular heart diseases, etc.....) • Familiar (one or more first-degree relatives) history of SCD • Unexplained syncope
48-hour ambulatory ECG	<ul style="list-style-type: none"> • Non-sustained ventricular tachycardia (NSVT)
Transthoracic Echocardiography (*rest and exercise)	<ul style="list-style-type: none"> • Maximal \geq LV wall thickness ≥ 30 mm • LVOT obstruction* • Left atrial diameter • LV apical aneurysm • LVEF $\leq 50\%$ (i.e., End-Stage evolution)
Cardiac Magnetic Resonance	<ul style="list-style-type: none"> • Maximal \geq LV wall thickness ≥ 30 mm • Left atrial diameter • Myocardial Fibrosis $\geq 15\%$ • LV apical aneurysm • LVEF $\leq 50\%$ (i.e., End-Stage evolution)
Exercise test	<ul style="list-style-type: none"> • Abnormal exercise blood pressure response
DNA analysis (NGS DNA)	<ul style="list-style-type: none"> • Particular mutation? • Double or Triple mutations?

SCD risk estimation is one of the most important aspects of the management of patient affected by HCM and it requires a comprehensive, meticulous and tailored assessment (**TABLE 1**)

Thus, the SCD accurate risk estimation can be extremely challenging and it recently became a source of argument between European and American experts. Although the main risk factor of SCD is definitely a previous resuscitated cardiac arrest, the identification of individuals at high risk of SCD in primary prevention is still a debated issue.

This is due to the fact that there are no randomized trials or statistically validated prospective prediction models in this field so that recommendations are based on observational, retrospective cohort studies.

Historically, five risk factors were considered at risk for SCD and the presence of 2 or more of these have been considered an indication for ICD implantation for primary prevention (Elliott, 2014., Gersh, 2011., Weissler-Snir, 2016.), i.e.,

1. familiar history of SCD
2. unexplained syncope
3. maximal left ventricular (LV) wall thickness ≥ 30 mm
4. non-sustained ventricular tachycardia (NSVT)
5. abnormal blood pressure response to exercise.

USA PERSPECTIVE

The 2011 ACCF/AHA guidelines have confirmed this old, timeworn and weakly evidence-based recommendation for implanting an ICD for primary prevention.

However, with respect to the previous 2003 ACC/ESC joint guidelines, in which the presence of two or more risk factors in a patient with HCM was considered an indication for ICD implantation for primary prevention, ACCF/AHA experts in 2011 have been assigned a major role to the first three risk factors that can be also present alone (Gersh, 2011.). Indeed, an international registry of 506 patients showed that within HCM patient who have received an ICD implantation, the number of risk factors did not correlate with the rate of subsequent appropriate device shocks (Maron, 2008.). However, it is important to notice that it is a very weak and retrospective evidence of a small cohort of patients and ICD shocks are not accurate surrogates of SCD; thus, generalising the results from these highly selected ICD cohorts to the general HCM population is questionable and contrary to the findings of larger, unselected HCM cohorts.

The upgrade of the first three factors as major factors sufficient to implant an ICD were not supported by any new significant evidence or prospective study.

Furthermore, a recent validation study was able to show that aggregation of single risk factors correlates with SCD more than one risk factor and the magnitude of the association of two or more risk factors with SCD is greater than that of a single risk factor (O'Mahony, 2011.). On the other hand, this study showed that the incidence of SCD in patients with a single risk factor is not significantly different from those without risk factor (O'Mahony, 2011.).

The historical approach has a significant number of limitations because it is based on old retrospective studies with small cohorts of patients that estimated only relative (and not absolute) risk and some risk factors – such as LV wall thickness – are treated as binary variables when they are associated with a continuous increase in risk.

Thus, ACCF/AHA 2011 guidelines can be easily and correctly defined as US expert opinions and recommendations on SCD risk evaluation, but it is not possible to affirm that those recommendations are evidence-based.

Literature suggests that strict compliance with the North American model could lead to ICD implantation in up to 40-60% of patient with HCM with a low annual rate of appropriate ICD shocks of about 2% in large HCM cohorts with implanted ICDs (O'Mahony, 2011., Maron, 2015., O'Mahony, 2012.).

Finally, it is important to note that US perspective is currently more receptive to new modifying risk factors than European perspective.

THE EUROPEAN PERSPECTIVE

On the other side of the Atlantic sea, the most recent (2014) ESC guidelines endorsed a new risk prediction model which includes 7 variables (Elliott, 2014., O'Mahony, 2014.), i.e.,

1. Age
2. Family history of SCD
3. Unexplained syncope
4. LV outflow tract obstruction
5. Maximal LV wall thickness
6. Left atrial diameter
7. NSVT

For the first time, European experts have done a significant change in the risk stratification of SCD in HCM, so that some authors defined this “a revolution” and some others “a significant evolution”.

The EU model was validated after a multicentre, retrospective cohort study of 3675 patients – defined as HCM Risk-SCD. This model gives a prognostic score and is

accessible as an online calculator. The HCM Risk-SCD uses variables that have been associated with an increased risk of SCD in at least one published multivariable analysis. Only four of the five classical risk factors passed the statistic exam of ESC and showed to be scientifically evidence-based. Moreover, the model provides individualised 5 years SCD risk estimation and, in a head to head comparison with a model using four major risk factors - very similar to the historical model – the performance of the prediction model significantly improved (C-index from 0.54 to 0.7). The HCM Risk-SCD compared favourably with other prediction algorithms such as the famous CHA₂DS₂-VASC.

The ESC HCM 2014 guidelines identify three risk zones, that are:

- Low Risk: 5-year risk < 4%
- Intermediate Risk: 5-year risk $\geq 4\%$ < 6%
- High Risk: 5-year risk $\geq 6\%$

Patients at high risk have a IIa class (“should be considered”) recommendation to implant an ICD, whereas patients at intermediate risk have a IIb class (“may be considered”) recommendation to implant an ICD. ICD is generally not indicated in patients at low risk.

The European model has the potential to reduce unnecessary and potentially harmful ICD implants in patients who do not suffer SCD and correctly identifying the majority who are most likely to benefit from an ICD.

At this point, it is important to note that the ESC guidelines change was well motivated and clearly evidence-based and offered a prediction model significantly more accurate with respect to the US model based on old-fashioned and little populations of patients.

Finally, 2014 ESC guidelines on HCM have been significantly improved prognostic SCD risk stratification and it represents a step forward in the current knowledge on SCD risk.

SCD RISK FACTORS

1. Prior Personal History of Resuscitated Cardiac Arrest

Patients with HCM who have experienced SCD or sustained VT represent the highest risk for subsequent malignant arrhythmogenic events. The rate per year of life-threatening arrhythmic events in this group of patients is 10% (Cecchi, 1989., Elliott, 1999., Maron, 2009.). As shown by three trials [Antiarrhythmic drugs Versus Implantable Defibrillator (AVID)(The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators 1997), Canadian Implantable Defibrillator Study (CIDS) (Connolly, 2000.),

and Cardiac Arrest Study Hamburg (CASH) (Kuck, 2000.). conducted in patients who had suffered a cardiac arrest or life-threatening ventricular arrhythmias (haemodynamically unstable ventricular tachycardia with syncope) - irrespective of the underlying cardiac disease - in which treatment with an ICD was compared with anti-arrhythmic drug therapy (predominantly amiodarone) the ICD reduced rates of arrhythmic mortality. Furthermore, a meta-analysis of the three trials demonstrated that ICD therapy was associated with a 50% (95% CI 0.37, 0.67; $P = 0.0001$) reduction in arrhythmic mortality and a 28% (95% CI 0.60, 0.87; $P = 0.006$) reduction in total mortality (Connolly, EHJ 2000.).

Thus, patients with a previous cardiac arrest or life-threatening ventricular arrhythmias (sustained VT) have the highest indication for ICD implantation (Class I) both in the European and in the US model.

2. Age

The effect of age on SCD has been explored in many studies over the last three decades. However, only recently a significant association between younger age and an increased SCD risk has been documented by three studies (O'Mahony, 2014., Elliott, 1999., Spirito, 2009.). Unexplained syncope, NSVT and severe LVH seems to be more important when associated with younger age. On the other hand, patients who are into the seventh decade of life have a low SCD risk even if associated with one classical risk factor (Spirito, 2009.).

3. Family History of SCD

One of the first observation in hypertrophic cardiomyopathy and generally in cardiovascular genetic diseases is that SCD events often cluster in families. Unfortunately, there are some conflicting data about this link in HCM due to the different definitions of familial SCD in the different studies. However, a family history of SCD is significant when one or more first degree relatives have died suddenly aged ≤ 40 years with or without a diagnosis of HCM, or when first-degree relatives with an established diagnosis of HCM have died suddenly at any age (Elliott, 2014). A recent meta-analysis – despite of the population heterogeneity of the different studies – was able to demonstrate an independent correlation between family history of SCD and SCD risk (Maron, 2013.).

4. Unexplained Syncope

Syncope (a temporary loss of consciousness secondary to transient, global cerebral hypoperfusion) is common in patient with HCM – it occurs in ~ 20-25% of patients – but is a challenging clinical differential diagnosis. There are multiple causes of syncope in HCM: atrial fibrillation, supraventricular tachycardias, bradyarrhythmias, sustained ventricular tachyarrhythmias, exercise-related LVOT obstruction, abnormal vascular responses, myocardial ischemia, neurally mediated syncope (vasovagal, situational and carotid sinus syncope) and orthostatic hypotension. Once the diagnosis of syncope is reached, identifying the cause relies exclusively on historical data provided by witnesses and patients.

Spirito et al. in 2009 defined unexplained as syncope “of unknown origin, when it occurred in circumstances not clearly consistent with a neurally mediated event, i.e., without apparent explanation at rest or during ordinary daily activities, or during an intense effort.

Several studies using survival analysis have shown a significant association of non-neurocardiogenic syncope - without an explanation after investigation - with an increased risk of SCD (Christiaans, 2010., Elliott, 2000., Efthimiadis, 2009., Elliott, 2006., Gimeno, 2009., Dimitrow, 2010.).

The strongest association between unexplained syncope and SCD comes from a large multicentre international study of 1511 HCM patients (Spirito, 2009.). In this cohort, relative risk of SCD was 1.78 (95% confidence interval 0.88 to 3.51, $P = 0.08$) in patients with unexplained syncope and 0.91 (95% confidence interval 0.00 to 3.83, $P = 1.0$) in those with neurally mediated syncope compared with patients without syncope. In particular, this association was significant only in patients with unexplained syncope within 6 months before the initial evaluation, showing a 5-fold increase in risk with respect to patients without syncope (adjusted hazard ratio 4.89, 95% confidence interval 2.19 to 10.94). Older patients (>40 years of age) with remote episodes of syncope (>5 years before initial evaluation) did not show an increased risk of SCD (adjusted hazard ratio 0.38, 95% confidence interval 0.05 to 2.74) (Spirito, 2009.).

5. LV Outflow Tract (LVOT) Obstruction

Several studies have demonstrated that LVOT obstruction is an independent predictor of adverse outcomes in patients with HCM (Veselka, 2016., Maron, 2003., Sorajja, 2009., Elliott, 2006.). These studies have demonstrated higher rates of SCD among patients with resting gradients ≥ 30 mmHg. It is important to notice that a previous study has showed not only this association but also a relationship between the severity of obstruction and the risk of SCD (Elliott, 2006.). Indeed, LVOT obstruction is not a binary variable but

it's associated with a continuous increase in risk (Elliott, 2006.). Thus, the higher the obstruction the higher SCD risk. A model that completely ignores the relationship between LVOT obstruction and SCD and that doesn't take into account it for the SCD risk stratification is inaccurate and approximate.

After a revision of the literature, the ESC decided to include this risk factor in its model and tested it in the previous mentioned multicentre international study, confirming a significant relationship between LVOT obstruction (at rest and with Valsalva provocation irrespective of concurrent medical therapy) and SCD and between the magnitude of LVOT obstruction and the risk of SCD (O'Mahony, 2014.).

However, the main doubts (or grey zones) about LVOT obstruction are the prognostic importance of provokable LVOT obstruction and the impact of LVOT obstruction treatment (medical vs alcohol septal ablation vs. surgical myectomy) on SCD risk.

6. Maximal LV Wall Thickness

An association between LV wall thickness - the greatest thickness in the anterior septum, posterior septum, lateral wall and posterior wall of the LV, measured at the level of the mitral valve, papillary muscles and apex using parasternal short-axis plane using 2D echocardiography - and risk of SCD has been clearly documented in a number of large studies, with a LV wall thickness ≥ 30 mm being shown as a risk factor of SCD (Spirito, 2000., Elliott, 2001.).

As well as: Age, LVOT obstruction and Left atrial diameter, LV wall thickness is a continuous and not binary variable, so the higher the hypertrophy the higher the SCD risk (Elliott, 2014., O'Mahony, 2014.).

It is important to recognize that risk does not automatically increase when wall thickness reaches a threshold of 30 mm, but like in all biological phenomenon increases in a linear fashion, so that a LV thickness of 29 mm is associated with a risk near equal to that related to 30 mm.

However, there are few data in patients with extreme hypertrophy (LV wall thickness ≥ 35 mm).

7. Left Atrial (LA) Diameter

Two different multicentre international retrospective studies have documented a clear independent association between LA diameter and SCD (O'Mahony, 2014., Spirito, 2009.). One of these is the previous mentioned retrospective cohort study of 3675 HCM patients carried out in Europe. There are no data on the association between SCD and LA

area or volume. Nonetheless, further studies using more accurate methods to measure LA with the purpose to investigate an independent association with SCD are warranted.

8. NSVT

Non-sustained ventricular tachycardia – defined as ≥ 3 consecutive ventricular beats at a rate of ≥ 120 beats per minute and < 30 s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation – is an independent and well documented predictor of SCD (O'Mahony, 2014., Elliott, 2008., Dimitrow, 2010., Monserrat, 2003.).

A percentage of 20-30% of HCM patients have a documented NSVT at Holter ECG. In contrast to the previous mentioned risk factors, NSVT is a binary variable. In other words, only the presence of ventricular tachycardia irrespective of frequency, duration or rate of NSVT is a risk factor for SCD.

9. Abnormal Blood Pressure Response to Exercise

Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterised by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve (Elliott, 2014). The most used definition of abnormal blood pressure response is the sequent: a failure pressure ≥ 20 mmHg from rest to peak exercise or a fall of > 20 mmHg from peak pressure. A very old monocentric study documented an association between an abnormal exercise blood pressure response and a higher risk of SCD in patients aged ≤ 40 years; however, this cohort included only 161 patients and investigating the 12 SCDs (3 in the normal blood pressure response group with respect to the 9 SCD in the abnormal blood pressure response group) all patients had other major risk factors such as: unexplained syncope, family history of SCD, LVOT obstruction, NSVT and all of these risk factors were associated to young age (Sadoul, 1997.). To sum up, this cohort had may bias and probably if we had the possibility to calculate the HCM Risk-SCD score it would have resulted in a 5-year risk $\geq 6\%$ irrespectively of the blood pressure response.

Finally, a recent study of 426 patients with HCM was able only to relate the abnormal blood pressure response to adverse outcomes (a composite endpoint of general death, appropriate internal defibrillator discharge, and hospitalization for heart failure) but not specifically to SCD (Desai, 2014.).

Thus, a clear documentation of an independent statistically significant association between abnormal blood pressure response and SCD does not yet exist in literature.

NEW MODIFYING RISK FACTORS AND NEW-ARBITRATORS

Over the last few years, cardiovascular research is going very fast in discovering new modifying risk factors. Thus, LV apical aneurysm, multiple sarcomere gene mutations, myocardial fibrosis (MF) and End-Stage (ES) HCM are becoming more and more important as final arbitrators especially in cases at intermediate risk.

1. LV Apical Aneurysm

LV Apical Aneurysm is considered a rare complication of HCM, one study reports a prevalence of 2.2% in the general HCM populations (Maron, 2008.). On the other hand, it is important to notice that this study reported an event rate of 10.5% per year of adverse cardiovascular events (SCD, appropriate ICD shocks, non-fatal thromboembolic stroke and progressive heart failure) that is very higher with respect to that of the general HCM population. In particular in this large series, 12 patients (43% of patients with LV Apical Aneurysm) experienced an adverse clinical event including: 2 SCD, 2 aborted cardiac arrest (1 patient presenting with ventricular fibrillation), appropriate ICD intervention for ventricular tachycardia/ventricular fibrillation (3 patients) and progressive heart failure. It is very important to notice that six of these 12 patients also developed ES-HCM (systolic dysfunction with a LV ejection fraction <50%) showing that this complication is related to ES-evolution and supporting the view of the LV apex as an Achille's heel in HCM hearts. Furthermore, most aneurysms have a scarred rim, which is associated with extensive areas of MF. Likewise, a very recent study showed a clear base-to-apex gradient in ES-HCM hearts with a significant increase in the amount of MF from the base toward the apex, which was severely affected by fibrosis (Galati, 2016.).

Thus, this study provided a proof of a link between LV Apical Aneurysm and ES-HCM, maybe related to MF (Galati, 2016.). However, the mechanism responsible for the formation of apical aneurysm in HCM is not yet understood.

It is important to highlight that this base-to-apex gradient is a distinctive feature of sarcomeric ES-HCM, especially when compared to other cardiomyopathies with a hypertrophic phenotype - cardiac amyloidosis in particular - where the LV apex is relatively spared by amyloid infiltration (Quarta, 2014.). Strain-rate evaluated by speckle tracking echocardiography can detect this feature and provide a useful clue for differential diagnosis (Quarta, 2014.).

2. Multiple Sarcomere Gene Mutations

Unless, during the past decades, many small studies were published regarding the association between some “malignant mutations” and adverse outcomes, these data were not confirmed later from other studies. On the other hand, over the last 5 years, many advances and steps forwards were done using the novel techniques of next generation DNA sequencing and conducting novel multicenter international studies.

Seven years ago, one study documented that HCM patients with double or triple mutations experience a worse prognosis compared with patients with a single mutation (Girolami, 2010.). Girolami et al. were able to demonstrate in a large cohort of 488 probands with HCM that the presence of rare triple sarcomere gene mutations correlates with heart failure, SCD and ES-HCM evolution.

Thus, this study provided a strong confirmation of other previous studies that in HCM does exist a “genetic burden” and this play a remarkable role in the phenotypic expression of HCM and in modifying the natural history of HCM (Girolami, 2010., Richard, 2003., Ingles, 2005., Maron, 2012.). These patients were younger and presented both a greater amount of myocardial fibrosis and a greater impairment of microvascular function due to adverse remodeling of the coronary arterioles.

Another more recent multicenter international study documented a complex genotypes prevalence (characterized by the coexistence of 2 or 3 mutations) of 13% in a cohort of 150 ES-HCM patients, i.e., a percentage threefold times higher than the values reported in the previous older literature for HCM patients (Biagini, 2014.). This study strengthened the hypothesis that the “genetic burden” contributes to disease severity and predicts ES evolution.

In 2010 Ho C et al. (Ho, 2010.) provided the first demonstration in humans that myocardial fibrosis develops not only in patients with overt HCM expression and with LGE at CMR, but also in sarcomeric mutation carriers without left ventricular hypertrophy. They were able to demonstrate – dosing the levels of serum C-terminal propeptide of type I procollagen (PICP) that indicate increased myocardial collagen synthesis – that myocardial fibrosis even precedes left ventricular hypertrophy.

Three years after, the same research group confirmed this observation, comparing different CMR techniques of tissue characterization, i.e., the T1 mapping methods vs LGE (Ho, 2013.). In this study T1 mapping method (pre- and postgadolinium) was the only one technique able to identify interstitial fibrosis not only in overt HCM patients and in sarcomere mutation carriers with left ventricular hypertrophy, but also in sarcomere mutation carriers without left ventricular hypertrophy, whereas LGE was able to identify replacement fibrosis only in overt HCM patients. Both T1 mapping and LGE were significantly more extensive in sarcomeric HCM. These findings documented that the fibrotic burden is higher in patients with HCM with sarcomere mutations compared with

those without a sarcomere mutation and could partly underlie the worse outcomes reported in sarcomere-positive versus sarcomere-negative HCM.

Therefore, these results could provide a link between myocardial fibrosis development in younger patients and SCD events that are related to the total amount of myocardial fibrosis.

Finally, in 2015, Lopes et al. showed in a large series (near 900 HCM patients) the first evidence that patients with sarcomeric protein gene mutations have higher cardiovascular and SCD-related mortality during their life with respect to HCM patients without sarcomeric protein gene mutations. However, it is important to notice that the low number of outcome events during follow-up may have biased the survival analysis in this study.

To sum up, nowadays, there isn't a clear evidence of relationship between some particular mutations and SCD in HCM patients and correctly it is impossible to include this variable in the SCD risk evaluation. Therefore, further prospective multicenter international studies are warranted.

In spite of that, it is necessary to take into account the "genetic burden" linked to adverse outcome in HCM patients, in particular in younger patients. Indeed, this patients with double or triple mutation needs of a very strict follow-up and of an early assessment for ICD implantation, because this is a strong modifying factor of the natural history of HCM.

3. Myocardial Fibrosis (MF)

In recent years, a relevant number of basic research and clinical studies have investigated the significance of MF in HCM. Both replacement and diffuse interstitial fibrosis type have been described as histologic hallmarks of disease. While replacement fibrosis has long been known to occur in HCM, particularly in ES-HCM (Moon, 2004.), it has only recently been shown that interstitial collagen deposition can occur in the very early stages of HCM and even precede the development of hypertrophy. Indeed fibrosis represents one of the primary phenotypic expressions of HCM and is not necessarily a time related complication (Ho, 2010., Ho, 2013.).

Fibroblasts and myofibroblasts have been identified as key fibrosis effectors in myocardium and as such are responsible for the synthesis of extracellular matrix proteins. An important role for fibroblasts proliferation in HCM-associated fibrosis has been suggested; in particular, signaling by transforming growth factor β (TGF β) seems to be important for activation of fibroblasts. In patients affected by HCM, the progressive accumulation of collagen results in fibrosis that could appear as diffuse interstitial-perimyocyte, dense and replacement ("scar-like") type or mixed type. Previous studies on murine models documented that the proliferation rate of fibroblasts, which occurs

independently of myocyte proliferation, is increased constantly in the hearts of mice that carry mutations in myosin-7 (Frey, 2011., Teekakirikul, 2010.). Furthermore, as previously written (see “Multiple Sarcomere Gene Mutations” paragraph) sarcomere gene mutation carriers express a profibrotic phenotype that becomes evident before the expression of hypertrophy and these subjects have a greater fibrotic burden than subjects without sarcomeric gene mutations.

However, the precise link between sarcomeric mutations and increased nonmyocyte proliferation it is not yet understood.

Fibrotic scarring in the heart correlates strongly with an increased incidence of arrhythmias and SCD.

The vast majority of data on MF in HCM are derived from CMR studies (Ho, 2013., Bruder, 2010., O’Hanlon, 2010., Adabag, 2008., Maron, 2008., Rubinshtein, 2010., Todiere, 2012., Prinz, 2013., Chan, 2014., Ismail, 2014., Green, 2012., Briasoulis, 2015.) or, indirectly, from the study of serum collagen turnover biomarkers such as MMP-1 (matrix metalloproteinase-1), PICP (C-terminal telopeptide of type I collagen), and TIMP-1 (tissue inhibitor of metalloproteinases-1) (Ho, 2010.).

A very recent study provided the best histological and histometric characterization of MF in ES-HCM and provided the most accurate comparison between LGE-CMR and histological quantification of MF (see ES-HCM paragraph) (Ho, 2010).

Furthermore, a large number of CMR studies (Bruder, 2010., O’Hanlon, 2010., Adabag, 2008., Maron, 2008., Rubinshtein, 2010., Todiere, 2012., Prinz, 2013., Chan, 2014., Ismail, 2014.) and two meta-analyses (Green, 2012., Briasoulis, 2015.) on the prognostic role of MF were published and they documented that MF is definitely an independent strong risk predictor of cardiovascular mortality and of SCD in HCM. In particular, a recent study showed that a LGE extent $\geq 15\%$ of the LV mass confer a >2 -fold risk of SCD and a LGE amount $\geq 20\%$ conveys a >3 -fold increase in risk of ES-HCM evolution (Chan, 2014.).

Despite of the well documented prognostic role of MF in HCM (the last meta-analysis considered 1414 patients without LGE and 1653 with LGE with an average follow-up of 3.05 years) (Briasoulis, 2015.), at the moment neither European guidelines neither American guidelines include it in the SCD risk factor. Nonetheless, it is important to underline that American guidelines acknowledge MF as a potential arbitrator, whereas European guidelines don’t include it in the prospective model.

This is a paradox if we notice that MF has been extensively studied over the last ten years and there are many studies and two meta-analyses about its prognostic role. Thus, the prognostic role of MF in HCM is even better evidence-based than some of the classical historical risk factors.

4. ES-HCM

The end-stage phase of HCM (or ES-HCM, or Hypokinetic-Dilated HCM evolution, Figure 3) is a rare complication of HCM (5% of all patients affected by HCM) defined as an LV ejection fraction $\leq 50\%$ at rest, reflecting global systolic dysfunction and carries an ominous prognosis (Harris, 2006., Biagini, 2005., Thaman, 2005., Biagini, 2008., Melacini, 2010.). The overall annual mortality rate of 11% per year is in sharp contrast to 1-2% per year for the overall HCM population, and is due to refractory heart failure and SCD. ES-HCM represents almost the only indication for heart transplantation in all centers of the world for patients affected by HCM (Harris, 2006., Biagini, 2005., Thaman, 2005., Biagini, 2008., Melacini, 2010.).

It is still debated whether the ES-HCM represents an indication in itself to ICD implantation.

Several different mechanisms have been proposed to explain the evolution toward ES, but the main mechanisms are two: myocardial fibrosis and microvascular ischemia. It has also been hypothesized that development of ES-HCM may be influenced by the specific genetic background (multiple sarcomere gene mutations).

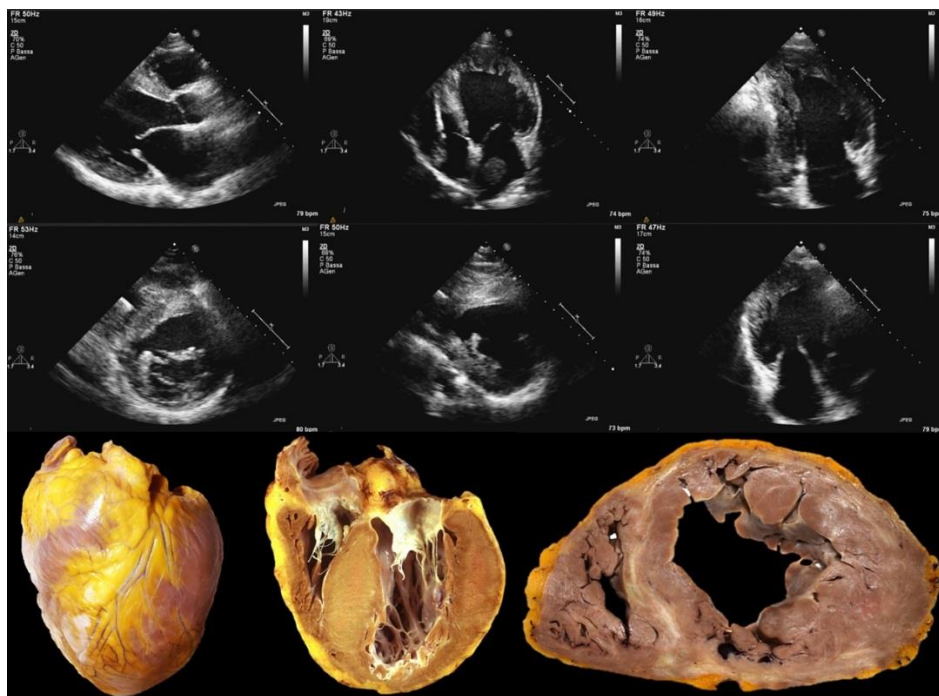


Figure 3. Echocardiographic and Pathological characteristics of End-Stage HCM (Dilated-Hypokinetic evolution). ES-HCM is characterized by a dilated and hypokinetic LV with thinned or normal left ventricular walls. Echocardiographic images show (in this case) a left atrial thrombus. Pathological images show fibrosis that is the white line inside myocardium.

Recently, an original multicenter european study provided the first detailed quantitative histological evaluation of extent, distribution, patterns and types of MF in a large population of ES-HCM explanted hearts. Moreover, it evaluated quantitative relationship between LGE-CMR assessment and histometric analysis of MF. It explored new perspectives on MF, on its imaging assessment and ultimately on the physiopathology of HCM and of SCD (Galati, 2016.).

Previously, detailed and systematic histological evaluations of quantitative and qualitative characteristics of MF in HCM lacked (there were only histological studies limited to single biopsy or to samples of the anterior-basal septum obtained during the myectomy). Furthermore, studies of correlation between histology and CMR were few and limited only to qualitative correlations.

For the first time this multicenter study provided some new amazing insights in this group of patients, i.e.,

- more than one third of LV myocardium (mean value of 37%) is replaced by fibrosis, so that the total amount of MF in these hearts is very high;
- a clear base-to-apex gradient is present with a significant increase in the amount of MF from the base toward the apex, which is always severely affected by MF in ES-HCM;
- inferior, anterior and anterolateral LV walls as well as interventricular septum are maximally affected by fibrosis, whereas the inferolateral LV wall is always relatively spared;
- the midwall layer is the most affected layer with respect to subepicardium, subendocardium and trabecular layer. Moreover, the predominant pattern is midwall, followed by midwall and subepicardial, by transmural and by midwall and subendocardial. The subendocardium and the subepicardium may be involved but never exclusively (Figure 4);
- in ES-HCM hearts there are at least three qualitative types of fibrosis, i.e., replacement (or scar-like), interstitial-perimyocyte and mixed fibrosis. Replacement fibrosis is the most represented type (Figure 5);
- younger patients had mixed fibrosis, both interstitial and scar-like, older patients showed only scar-like fibrosis that is typical of the more advanced stage of the disease;
- there is a tight proximity between areas of scar-like fibrosis and abnormal arterioles in different sections. Furthermore, hypertrophy of the media and hyperplasia of intima produce coronary microvascular dysfunction and are a potential cause of myocardial ischemia;
- there is a good overlap between LGE-CMR and histological quantification of MF. However, LGE underestimated fibrosis extent in patients who have mainly interstitial-perimyocyte MF, showing that LGE is able to identify only dense

scars but cannot capture more diffuse expansion of the extracellular space, such as that is caused by interstitial fibrosis.



Figure 4. Myocardial fibrosis distribution across an ES-HCM explanted heart at midventricular section. Azan-Mallory trichrome staining. Fibrosis is coloured in blue, whereas myocardium is coloured in pink/red. Notice circumferential distribution of fibrosis which is predominantly midwall in this case. Subepicardium and subendocardium could be involved, but never exclusively (From Galati et al) (Galati 2016).

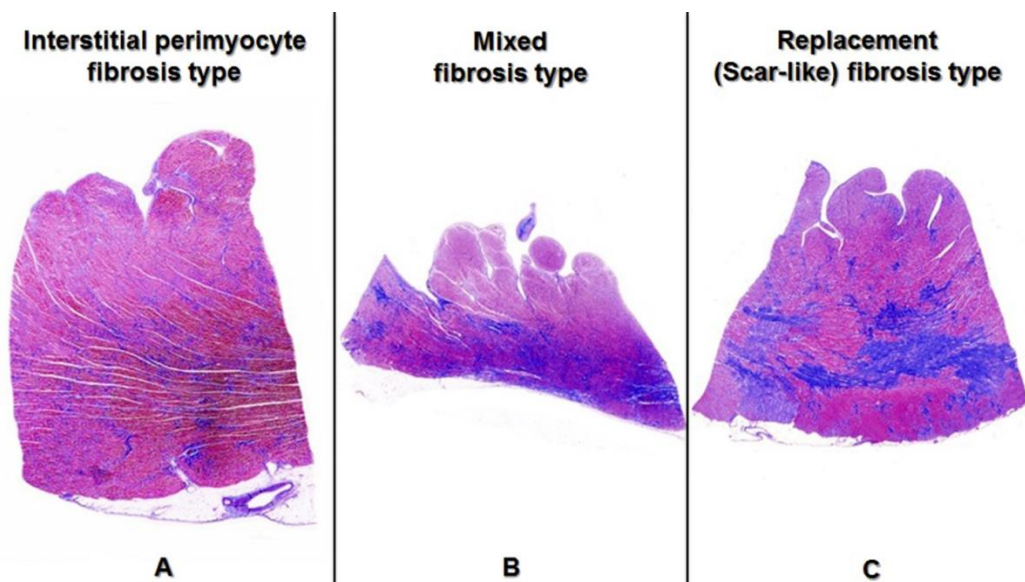


Figure 5. Different types of myocardial fibrosis in ES-HCM (from Galati et al) (Galati 2016).

To sum up ES-HCM patients have a LGE extent >20% of the LV mass and this added to myocardial ischemia phenomena provides an explanation of the high rate of the annual mortality due to both SCD and to refractory heart failure.

Finally, it is important to notice that prospective studies in ES-HCM patients are lacking, but nowadays ES-evolution it's quite unpredictable (ES-HCM and SCD familiarity are the strongest risk factors), and usually is very fast - the mean time from ES identification to death or transplantation is often three years in all the major published series - therefore it's very difficult to design a prospective study. The problem of small sample size is inherent to the rarity of ES evolution with respect to the total population affected by HCM and larger studies of this kind are unlikely to be conducted.

However, tertiary referral centers which deal with these patients usually indicate an ICD implantation in primary prevention, because ES-HCM patients are very young and generally within 3 years they will undergo a heart transplantation. Therefore, the risk of infective endocarditis in these patients is very low and the potential benefit is very high or inestimable (i.e., escape from SCD where your patient is in the waiting list for heart transplantation).

Another point that deserves to be mentioned is the role for cardiac resynchronization therapy (CRT) in this subset of patients. A very recent retrospective study, published in 2016 and conducted in USA (Killu, 2016.), showed no benefits in patients with CRT-D with respect to the control group. There was not any outcome benefits and CRT-D failed also to slow the progression of the disease, thus, like in patients without CRT-D the time from ES-HCM diagnosis to Heart transplantation or Left ventricular assist device implantation was three years. Even left ventricular ejection fraction remained the same unless the electrophysiological parameters for CRT-D implantation were respected (i.e., the baseline QRS duration was 182 ± 39 msec, with left or right bundle branch morphology and no atrial fibrillation in implanted population). This could be explained by the very high amount of myocardial fibrosis in these hearts, so it is impossible for an electrical therapy to resynchronize scars that substitutes a such relevant percentage of myocardium.

KEY MESSAGES

SCD risk estimation is one of the most difficult topics of the entire cardiology. This is due to several factors:

- The HCM population, that is younger with respect to the rest of the cardiovascular population, therefore the decision to implant or not to implant an ICD have a major impact on life of these patients and only one mistake could be catastrophic.

- The management of patient affected by HCM requires a comprehensive, meticulous and tailored assessment that couldn't be done by a single cardiologist or a single electrophysiologist in whatever center, but only by a team of cardiologists with a proven expertise in myocardial and pericardial diseases who work in referral centers for HCM.
- The risk evaluation is complex due to the lack of prospective studies.
- Unfortunately, an international consensus about the SCD risk assessment is still lacking and the world about this argument is almost split in two perspectives: the American and the European perspective.
- Taking into account all these difficulties and effort and a step forward must be done. One of the crucial point is the correct interpretation of the historical risk factors under the light of contemporary evidence and the implementation of the new risk factors that it is impossible to ignore. Therefore, is not important to share American or European position, because no one is the owner of the truth. We need to take decisions and to manage HCM patients on the basis of the strongest evidences. Thus, currently literature shows that the European model is more accurate and it evaluates better SCD risk with respect to the old American model.
- On the other hand, the new modifying risk factors are amazingly important and American experts are more aware of these with respect to the European experts. Therefore, the vast majority of HCM referral centers consider the total amount of LGE and myocardial fibrosis as an important modifying risk factor able to influence the decision to implant or not to implant an ICD.
- HCM dedicated centers worldwide should collaborate and conduct international prospective multicenter studies with the purpose to discover reliable predictors of SCD in HCM and enable better evidence-based decisions.
- The need of an international agreement is a compelling issue that can't be further postponed. Thus, the purpose of this chapter is not only to make a review of the old management of SCD risk in HCM patients, but also to particularly focus on the new modifying risk factors and to future perspectives. Then, the aim is to underline that there is a great work and research to do in this field and it cannot be done by one single center or by a single country (because in science and in medicine nobody come first, therefore "not America first", "not Europe first", but "the world comes first").

FUTURE PERSPECTIVES

An extraordinary effort should be done in the understanding of myocardial fibrosis and the link between genetics, myocardial fibrosis and myocardial ischemia.

Many studies were cited previously in this chapter that highlighted the remarkable importance of fibrosis about the pathogenesis of HCM, SCD and ES-HCM evolution.

1. Research on Myocardial Fibrosis

One of the most relevant hypotheses endorsed by several studies (both in murine models and in humans) is that specific pathogenic mutations not only of sarcomere genes but also of genes which encodes for extracellular matrix proteins – and that regulate fibroblasts and myofibroblasts proliferation – stimulate both collagen synthesis, fibroblast proliferation (causing an early profibrotic cardiac remodelling that precedes left ventricular hypertrophy) and coronary microvascular dysfunction characterized by intimal hyperplasia and by medial hypertrophy that leads to the reduction and sometimes to the obliteration of the vessel lumen (Figure 6). These features are more conspicuous in younger patients and in ES-HCM, as well documented by one previously cited study.

Following this thesis (Figure 7), during early stages fibrosis develops as interstitial-perimyocyte fibrosis and can be detected only by the novel T1 mapping CMR methods or by dosing specific collagen turnover biomarkers (like PICP, etc.). The disease gradually worsens and interstitial fibrosis converges in areas of dense scar or replacement fibrosis. When the total amount of fibrosis reach a certain extent and a critical threshold (typically $\geq 15\%$ of the LV mass), major arrhythmic events responsible of SCD arise.

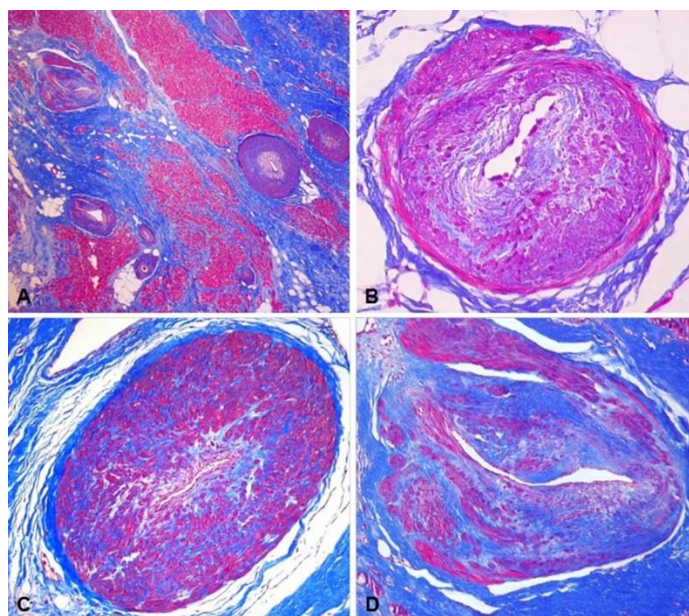


Figure 6. Abnormal intramural coronary arteries associated with replacement fibrosis (from Galati et al.) (Galati 2016).

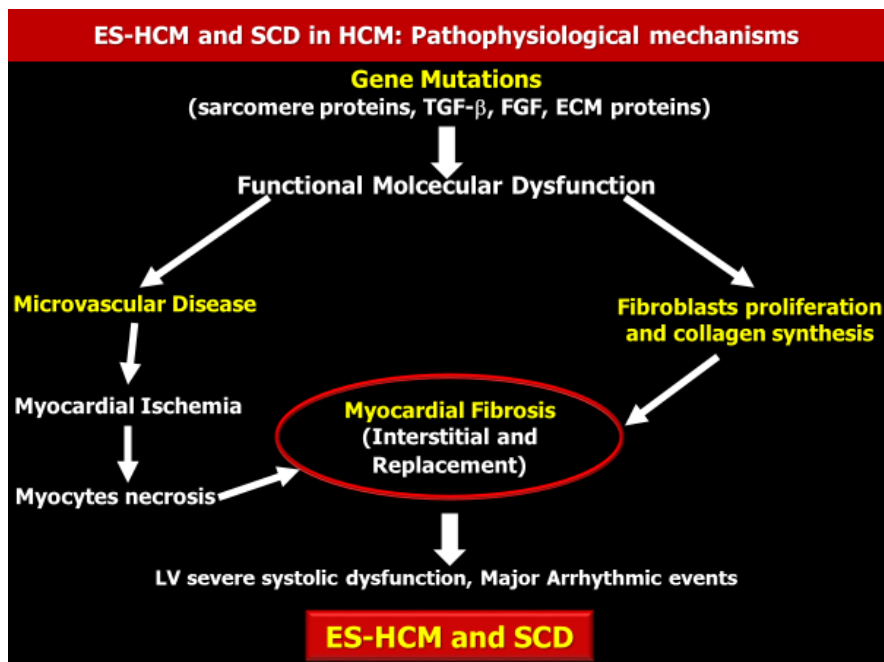


Figure 7. Pathophysiological Mechanisms of SCD and ES-HCM evolution in HCM patients.

Moreover, further progression of fibrosis – in particular subjects genetically predisposed – and of coronary microvascular abnormalities causes induces the most ominous evolution, i.e., ES-HCM evolution. A key role in this process is played by TGF- β .

Another important point to underline is that a large number of studies shows that MF initially affects midwall layer and later - depending upon the prevailing pathogenetic mechanism (myocardial ischemia, collagen production and fibroblasts' proliferation) - sometimes it extends at subepicardium sometimes at subendocardium and in advanced cases becomes transmural. This feature clearly distinguishes sarcomeric ES-HCM from ischemic heart disease - where fibrosis is mainly subendocardial and it spreads from subendocardium towards subepicardium - and from arrhythmogenic cardiomyopathy where fibrosis is mainly subepicardial with a subepi-subendo progression (Galati, 2016.). The reason of the major involvement of midwall layer as well as the apex with respect to the base is not yet understood. Therefore, research in this field and the understanding of molecular mechanisms which are the basis of the excessive and pathological fibrosis production could lead cardiovascular science to discover new specific therapies, targeted to block or reduce fibrosis development. A clear example could be the development of new monoclonal antibodies that block TGF- β or proteins and genes involved in fibrosis production.

2. Research on Myocardial Ischemia and Microvascular Dysfunction

Starting from post-mortem studies of small series of patients who had died suddenly, during the last decade, autopsy studies in HCM patients have documented coronary microvascular pathology characterized by intimal hyperplasia and tunica media hypertrophy that causes luminal area reduction of intramural coronary arterioles and sometimes lumen obliteration.

In 2003, Cecchi et al. provided the first evidence that ischemia has significant prognostic consequences in HCM. Indeed, using NH13-Positron Emission Tomography (PET) with dipyridamole injection they documented – in a cohort of 51 HCM patients followed for more than 8 years – that myocardial blunted blood flow proved to be an independent predictor of cardiovascular mortality (due to SCD or to refractory heart failure) (Cecchi, 2003.).

Indeed, areas of fibrosis originating from the replacement of necrotic or apoptotic cardiomyocytes are considered to be a potential morphological marker of microischemia-triggered arrhythmias.

Following multicenter studies on larger HCM patient series (Maron, 2009., Olivotto, 2011., Olivotto, 2006., Petersen, 2007.) confirmed this finding not only using PET but also CMR, in particular they were able to demonstrate a relationship between severe microvascular abnormalities, severe myocardial ischemia and ES-HCM evolution leading to refractory heart failure.(Cecchi, 2003., Olivotto, 2006.).

Furthermore, recently, it was proved that patients with sarcomere myofilament gene mutations – in particular those with MYH7 mutations and patients with double or triple mutations – with respect of patients without sarcomere gene mutations showed more significant microvascular ischemia due to a more severe pathology of small coronary vessels (Maron, 2009., Olivotto, 2011.).

CMR studies proved that myocardial blood flow was reduced to a greater degree in the subendocardium, and area of microvascular ischemia were associated to LGE.

Finally, a previous mentioned study, confirmed these observation from a histopathological point of view, documenting a close relationship between major coronary microvascular pathology and the development of replacement fibrosis.

The most accredited hypothesis is that pathogenic mutations who involve system of pro-epicardial origin such as cells which form coronary vessels, mitral valve and the fibrous heart skeleton are able to cause all the histopathologic abnormalities observed in HCM patients (Maron, 2009., Olivotto, 2011., Olivotto, 2006., Petersen, 2007.).

However, further studies are warranted in this field, because this is another remarkable phenomenon that could be a potential therapeutic target.

3. Research on Genetics

Beyond the cardiomyocyte-centric view of heart injury, it is now accepted that alterations of the cardiac extracellular matrix (ECM) and cardiac remodeling play a major role in the development and evolution of cardiac diseases leading to SCD and heart failure.

Across this chapter, we often cited and pointed out the major role that mutations of gene which regulates ECM and fibroblast proliferation play in the development of myocardial fibrosis and on the HCM phenotype.

Likewise, similar gene could be responsible of pathology of intramural coronary arterioles as well as some specific sarcomere gene mutations. Moreover, we mentioned also the role of double and triple mutation – i.e., the concept of the “genetic burden”.

Add to this, another aspect deserves to be mentioned. Recently, a multicenter italian study (Biagini, 2016.) documented that “a pseudo-STEMI” electrocardiographic pattern, QRS duration ≥ 120 msec and prolonged QTc interval are independent predictors of SCD and major cardiovascular events (appropriate implanted cardiac defibrillator discharge, resuscitated cardiac arrest, death due to heart failure, cardioembolic stroke, or heart transplantation). This preliminary finding need to be confirmed by further international multicenter studies.

However, this phenomenon could be explained by coexistence of sarcomere gene mutations and ion channels mutations that could affect a selected HCM population and could lead to a particularly early SCD.

Indeed, electrocardiogram remain a tool with high sensitivity in myocardial diseases and it is able to detect major changing in the myocardium. For example, ES-HCM patients very often shows the “arrow sign” at electrocardiogram (Figure 8), that usually is identifiable before the echocardiographic diagnosis (Oreto, 2009.).

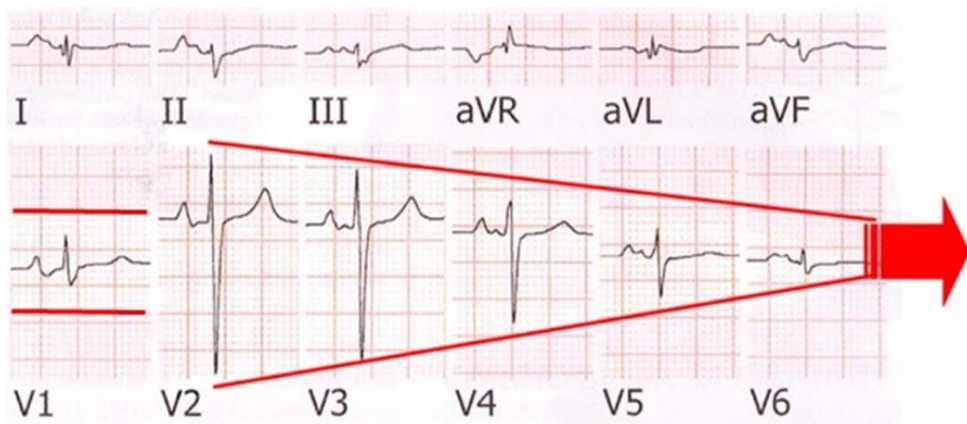


Figure 8. “The arrow sign”. Precordial leads placed side by side draw an arrow tip. While V1 represents the arrow shaft (From Oreto) (Oreto 2009).

Finally, the novel next generation sequencing techniques (NGS) and the new growing expertise required to understand the results of NGS will allow myocardial disease experts to discover and to better understand the role of genetics in HCM pathophysiology, especially in SCD pathophysiology.

REFERENCES

- Adabag, A. S., Maron, B. J., Appelbaum, E., et al. (2008). Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol*, 51, 1369-1374.
- Biagini, E., Coccolo, F., Ferito, M., et al. (2005). Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. *J Am Coll Cardiol*, 46, 1543-1550.
- Biagini, E., Olivotto, I., Iascone, M., et al. (2014). Significance of sarcomere gene mutations analysis in the end-stage phase of hypertrophic cardiomyopathy. *Am J Cardiol*, 114, 769-776.
- Biagini, E., Pazzi, C., Olivotto, I., et al. (2016). Usefulness of electrocardiographic patterns at presentation to predict long-term risk of cardiac death in patients with hypertrophic cardiomyopathy. *Am J Cardiol*, 118, 432-9.
- Biagini, E., Spirito, P., Leone, O., et al. (2008). Heart Transplantation in Hypertrophic Cardiomyopathy. *Am J Cardiol*, 101, 387-392.
- Briasoulis, A., Mallikethi-Reddy, S., Palla, M., et al. (2015). Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. *Heart*, 101, 1406-11.
- Bruder, O., Wagner, A., Jensen, C. J., et al. (2010). Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 56, 875-887.
- Cecchi, F., Maron, B. J. & Epstein, S. E. (1989). Long-term outcome of patients with hypertrophic cardiomyopathy successfully resuscitated after cardiac arrest. *J Am Coll Cardiol*, 13, 1283-8.
- Cecchi, F., Olivotto, I., Gistri, R., et al. (2003). Coronary microvascular dysfunction and prognosis in hypertrophic cardiomyopathy. *N Engl J Med*, 349, 1027-35.
- Chan, R. H., Maron, B. J., Olivotto, I., et al. (2014). Prognostic Value of Quantitative Contrast-Enhanced Cardiovascular Magnetic Resonance for the Evaluation of Sudden Death Risk in Patients With Hypertrophic Cardiomyopathy. *Circulation*, 130, 484-495.
- Christiaans, I., van Engelen, K., van Langen, I. M., et al. (2010). Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. *Europace*, 12, 313-321.

- Connolly, S. J., Gent, M., Roberts, R. S., et al. (2000). Canadian implantable defibrillator study(CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation*, 101, 1297-1302.
- Connolly, S. J., Hallstrom, A. P., Cappato, R., et al. (2000). Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J*, 21, 2071-2078.
- Desai, M. Y., Bhonsale, A., Patel, P., et al. (2014). Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging*, 7, 26–36.
- Dimitrow, P. P., Chojnowska, L., Rudzinski, T., et al. (2010). Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a new model of maximalized follow-up. *Eur Heart J*, 31, 3084-3093.
- Efthimiadis, G. K., Parcharidou, D. G., Giannakoulas, G., et al. (2009). Left ventricular outflow tract obstruction as a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. *Am J Cardiol*, 104, 695-699.
- Elliott, P., Andersson, B., Arbustini, E., et al. (2008). Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*, 29, 270-276.
- Elliott, P. M. (2016). Hypertrophic Cardiomyopathy: Job Done or Work in Progress? *J Am Coll Cardiol*, 67, 1410-11.
- Elliott, P. M., Anastakis, A., Borger, M. A., et al. (2014). 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*, 35(39), 2733-79.
- Elliott, P. M., Gimeno Blanes, J. R., Mahon, N. G., et al. (2001). Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet*, 357, 420-424.
- Elliott, P. M., Gimeno, J. R., Tomé, M. T., et al. (2006). Left ventricular outflow tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. *Eur Heart J*, 27, 1933-1941.
- Elliott, P. M., Poloniecki, J., Dickie, S., et al. (2000). Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol*, 36, 2212-2218.
- Elliott, P. M., Sharma, S., Varnava, A., et al. (1999). Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 33, 1596-601.
- Frey, N., Luedde, M. & Katus, H. A. (2011). Mechanisms of disease: hypertrophic cardiomyopathy. *Nat Rev Cardiol*, 9, 91-100

- Galati, G., Leone, O., Pasquale, F., et al. (2016). Histological and Histometric characterization of myocardial fibrosis in End-Stage hypertrophic cardiomyopathy: A Clinical-Pathological Study of 30 Explanted Hearts. *Circ Heart Fail*, Sep, 9(9). pii: e003090.
- Gersh, B. J., Maron, B. J., Bonow, R. O., et al. (2011). 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, 58, e212-60.
- Gimeno, J. R., Tome-Esteban, M., Lofiego, C., et al. (2009). Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Eur Heart J*, 30, 2599-2605.
- Girolami, F., Ho, C. Y., Semsarian, C., et al. (2010). Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. *J Am Coll Cardiol*, 55(14), 1444-53.
- Green, J. J., Berger, J. S., Kramer, C. M. & Salerno, M. (2012). Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging*, 5, 370-377.
- Harris, K. M., Spirito, P., Maron, M. S., et al. (2006). Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation*, 114, 216-25.
- Ho, C. Y., Abbasi, S. A., Neilan, T. G., et al. (2013). T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. *Circ Cardiovasc Imaging*, 6, 415-422.
- Ho, C. Y., López, B., Coelho-Filho, O. R., et al. (2010). Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. *N Engl J Med*, 363, 552-63.
- Ingles, J., Doolan, A., Chiu, C., et al. (2005). Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. *J Med Genet*, 42, e59.
- Ismail, T. F., Jabbour, A., Gulati, A., et al. (2014). Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. *Heart*, 100, 1851-1858.
- Killu, A. M., Park, J. Y., Sara, J. D., et al. (2016). Cardiac resynchronization therapy in patients with end-stage hypertrophic cardiomyopathy. *Europace*, 0, 1-7.
- Kuck, K. H., Cappato, R., Siebels, J. & Ruppel, R. (2000). Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation*, 102, 748-754.

- Lopes, L. R., Syrris, P., Guttman, O. P., et al. (2015). Novel genotype–phenotype association demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. *Heart*, 101, 294-301
- Maron, B. J., Haas, T. S., Shannon, K. M., et al. (2009). Long-term survival after cardiac arrest in hypertrophic cardiomyopathy. *Heart Rhythm*, 6, 993-7.
- Maron, B. J., Maron, M. S. & Semsarian, C. (2012). Double or compound sarcomere mutations in hypertrophic cardiomyopathy: a potential link to sudden death in the absence of conventional risk factors. *Heart Rhythm*, 9, 57-63.
- Maron, B. J., Rowin, E. J., Casey, S. A., et al. (2013). Risk stratification and outcome of patients with hypertrophic cardiomyopathy \geq 60 years of age. *Circulation*, 127, 585-593.
- Maron, B. J., Rowin, E. J., Casey, S. A., et al. (2015). Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol*, 65, 1915-28.
- Maron, M. S., Appelbaum, E., Harrigan, C. J., et al. (2008). Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. *Circ Heart Fail*, 1, 184-191.
- Maron, M. S., Finley, J. J., Bos, J. M., et al. (2008). Prevalence, clinical Significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation*, 118, 1541-1549.
- Maron, M. S., Olivotto, I., Betocchi, S., et al. (2003). Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *New Engl J Med*, 348, 295-303.
- Maron, M. S., Olivotto, I., Maron, B. J., et al. (2009). The case for myocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 54, 866-75.
- Maron, M. S., Olivotto, I., Zenovich, A. G., et al. (2006). Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation*, 114, 2232-2239.
- Maron, M. S., Rowin, E. J., Olivotto, I., et al. (2016). Contemporary Natural History and Management of Nonobstructive Hypertrophic Cardiomyopathy. *J Am Coll Cardiol*, 67, 1399-409.
- Melacini, P., Basso, C., Angelini, A., et al. (2010). Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. *Eur Heart J*, 31, 2111-2123.
- Monserrat, L., Elliott, P. M., Gimeno, J. R., et al. (2003). Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol*, 42, 873-879.
- Moon, J. C., Reed, E., Sheppard, M. N., et al. (2004). The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 43, 2260-4.

- O'Hanlon, R., Grasso, A., Roughton, M., et al. (2010). Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 56: 867-874.
- O'Mahony, C., Jichi, F., Pavlou, M., et al. (2014). A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). *Eur Heart J*, 35, 2010-201.
- O'Mahony, C., Lambiase, P. D., Quarta, G., et al. (2015). The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart*, 98, 116-25.
- O'Mahony, C., Tome-Esteban, M., Lambiase, P. D., et al. (2013). A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Heart*, 99, 534-541.
- Olivotto, I., Cecchi, F., Gistri, R., et al. (2006). Relevance of coronary microvascular flow impairment to long-term remodeling and systolic dysfunction in hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 47, 1043-1048.
- Olivotto, I., Girolami, F., Sciagrà, R., et al. (2011). Microvascular function is selectively impaired in patients with hypertrophic cardiomyopathy and sarcomere myofilament gene mutations. *J Am Coll Cardiol*, 58, 839-48.
- Oreto, Giuseppe., et al. (2009). L'elettrocardiogramma un mosaico a 12 tessere. Torino: Centro Scientifico Editore, 2009.
- Petersen, S. E., Jerosch-Herold, M., Hudsmith, L. E., et al. (2007). Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. *Circulation*, 115, 2418-2425.
- Prinz, C., Schwarz, M., Ilic, I., et al. (2013). Myocardial fibrosis severity on cardiac magnetic resonance imaging predicts sustained arrhythmic events in hypertrophic cardiomyopathy. *Can J Cardiol*, 29, 358-363.
- Quarta, C. C., Solomon, S. D., Uraizee, I., et al. (2014). Left Ventricular Structure and Function in Transthyretin-Related Versus Light-Chain Cardiac Amyloidosis. *Circulation*, 129, 1840-1849.
- Richard, P., Charron, P., Carrier, L., et al. (2003). Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*, 107, 2227-2232.
- Rubinshtein, R., Glockner, J. F., Ommen, S. R., et al. (2010). Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail*, 3, 51-58.
- Sadoul, N., Prasad, K., Elliott, P. M., et al. (1997). Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation*, 96, 2987-2991.

- Semsarian, C., Ingles, J., Maron, M. S., et al. (2015). New Perspectives on the Prevalence of Hypertrophic Cardiomyopathy. *J Am Coll Cardiol*, 65, 1249-54.
- Sorajja, P., Nishimura, R. A., Gersh, B. J., et al. (2009). Outcome of mildly symptomatic or asymptomatic obstructive hypertrophic cardiomyopathy: a long-term follow-up study. *J Am Coll Cardiol*, 54, 234-41.
- Spirito, P., Autore, C., Rapezzi, C., et al. (2009). Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation*, 119, 1703-10.
- Spirito, P., Bellone, P., Harris, K. M., et al. (2000). Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med*, 342, 1778-1785.
- Teekakirikul, P., Eminaga, S., Toka, O., et al. (2010). Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires TGF- β . *J Clin Invest*, 120, 3520-3529.
- Thaman, R., Gimeno, J. R., Murphy, R. T., et al. (2005). Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. *Heart*, 91, 920-925.
- The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators, (1997). A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*, 337, 1576-1583.
- Todiere, G., Aquaro, G. D., Piaggi, P., et al. (2012). Progression of myocardial fibrosis assessed with cardiac magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol*, 60, 922-9.
- Veselka, J., Jensen, M. K., Liebrechts, M., et al. (2016). Low procedure-related mortality achieved with alcohol septal ablation in European patients. *Int J Cardiol*, 209, 194-95.
- Weissler-Snir, A., Adler, A., Williams, L., et al. (2016). Prevention of sudden death in hypertrophic cardiomyopathy: bridging the gaps in knowledge. *Eur Heart J*, Jul 1. pii: ehw268.

Chapter 8

CHAGAS CARDIOMYOPATHY AS ONE OF THE LEADING CAUSES OF SUDDEN CARDIAC DEATH IN THE HISPANIC POPULATION

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ABSTRACT

Sudden cardiac death has been a major cause of death in Latin American countries and becoming a real problem in public health. In the Hispanic population common causes of SCD include coronary artery disease (CAD), Chagas disease and idiopathic dilated cardiomyopathy. Dubner et al. identified independent risk factors for mortality included age >70 years old, male gender, NYHA III/IV, and ejection fraction <30%. The etiology of the disease (Chagas vs CAD) was not found to be a risk factor.

This condition is apparently not well understood by health care professionals of Latin American countries. Gonzalez-Zuelgaray et al. demonstrated through the PLASMA (Probabilidad de sufrirmuertearritmica) study that international guidelines for primary prevention ICD implantation are not well followed. Around 13% of patients meeting the international ICD guidelines criteria were prescribed an ICD and the primary reason of this was general cardiologists did not perceive that these patients actually met the criteria to receive an ICD even when the collected evidence suggested that. This fact could be an important cause for the high mortality associated to SCD in Hispanics. For that reason, constant updating of general practitioners and subspecialists like cardiologists is important to reduce bad outcome and start to incorporate preventable measures in this population.

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SUDDEN CARDIAC DEATH (SCD)

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes that occurs in a short period of time (usually within 1 hour of symptom onset) in a person with known or unknown cardiac disease.

Signs and Symptoms

Usually these patients have prodromes of chest pain, fatigue, palpitations and other non-specific complaints. It is important to describe the factors relating to coronary artery disease (CAD) and myocardial infarction (MI) and ischemic cardiomyopathy include the following:

- Family history of premature coronary artery disease.
- Smoking.
- Dyslipidemia.
- Hypertension.
- Diabetes.
- Obesity.
- Sedentary lifestyles.

Risk factors for coronary artery disease include:

- Previous cardiac arrest.
- Syncope.
- Prior myocardial infarction (MI), especially within 6 months.
- Ejection fraction less than 30-35%.
- History of frequent ventricular ectopy.

The most common electrophysiologic mechanisms leading to SCD are tachyarrhythmias such as ventricular fibrillation or ventricular tachycardia. Interruption of tachyarrhythmias, such as an automatic external defibrillator or implantable cardioverterdefibrillator has been shown to be effective in the treatment of ventricular fibrillation and ventricular tachycardia. The implantable defibrillator has become the central therapeutic factor in prevention and treatment of sudden cardiac death. 20 to 30% of patients with documented sudden cardiac death events have bradyarrhythmia or asystole at the time of initial contact. Most cases of SCD occur in patients with structural

abnormalities of the heart. Myocardial infarction (MI) and post-MI remodeling of the heart is the most common structural abnormality in patients with SCD.

Hypertrophic cardiomyopathy and dilated cardiomyopathy are associated with an increased risk of SCD. Various valvular diseases such as aortic stenosis are associated with increased risk of SCD. The strongest known predictor of SCD is significant left ventricular dysfunction of any cause.

Epidemiology of Sudden Cardiac Death (SCD) in Latin America

Sudden cardiac death has been a major cause of death in Latin American countries and it is becoming a real problem in public health. In the Hispanic population common causes of SCD include coronary artery disease (CAD), Chagas disease and idiopathic dilated cardiomyopathy. Dubner identified independent risk factors for mortality included age >70 years old, male gender, NYHA III/IV, and ejection fraction <30%. The etiology of the disease (Chagas vs CAD) was not found to be a risk factor.

This condition is apparently not well understood by health care professionals of Latin American countries. Gonzalez-Zuelgaray demonstrated through the PLASMA (Probabilidad de sufrirmuertearritmica) study that international guidelines for primary prevention ICD implantation are not correctly implemented in Latin American countries. Around 13% of patients that meet the international ICD guidelines criteria were prescribed an ICD and the reason about why low percentage of patients were not started on ICD was that general cardiologists were not trained properly about the criteria that patients must have to receive an ICD, even when the collected evidence suggested that. This fact could be an important cause for the high mortality associated to SCD in Hispanics. Because of that continue medical education physicians, primary care doctors and subspecialists like cardiologists, is important in order to reduce this outcome and start to incorporate preventable measures in this population.

History of Chagas Disease in Latin America: A Brief Summary

- Chagas disease became visible as a major public health problem 25 years after Chagas's discovery, relying on specific historic achievements:
- Description of the Romaña sign (1934) promotes and facilitates the discovery of hundreds of cases of acute disease in several countries.
- Improvement and availability of serological diagnosis by complement fixation test based on the research carried out at the Oswaldo Cruz Institute and São Paulo Medicine School between 1944 and 1950.

- Achievement of serological screening of the general population in endemic areas of Minas Gerais and São Paulo (Brazil) in 1946.
- Pioneer studies associating serology and electrocardiography in the same endemic regions in 1947;
- Serological screening at blood banks in Belo Horizonte, São Paulo, and Venezuela in 1949.
- Progressive clarification and systematization of chronic cardiomyopathy, started by Laranja in Bambuí between 1946 and 1955.
- Systematization of Chagas chronic heart disease published in *Circulation* in 1956.
- Clinical and pathological studies about the digestive form of chronic HCD started in 1955 in Ribeirão Preto and Goiás (Brazil),
- International congresses and meetings on HCD in 1959 (Rio), 1960 (Washington), 1970 (Caracas), 1975 (Belo Horizonte), and 1979 (Rio).
- Improvement of serology since the 1960s with the development of new modern, easier, and more reliable techniques such as hemagglutination and indirect immunofluorescence.
- Creation of medical institutes to stimulate and support researches in HCD from the 1970s, such as Brazil's PIDE/CNPq (Integrated Program on Endemic Diseases/Brazilian National Research Council), the World Health Organization (WHO)'s TDR (Tropical Disease Research), and CONICIT (Science and Technology National Council) in Argentina and Venezuela among others.
- National serological surveys of disease prevalence in São Paulo, the rest of Brazil, Venezuela, and Argentina, between 1965 and 1985.
- The first epidemiologic studies on the medical impact of vector control, carried out in São Paulo, Bambuí, and Venezuela, in the 1970s.

In the 1970s a general framework on the prevalence, distribution, and medical importance of Chagas disease was outlined, incorporating both the arguments and epidemiological data necessary for control programs. Prevalence was estimated at approximately 15 million infected in Latin America. In Brazil, there are an estimated 5 million cases, with an incidence rate of 100,000 new cases annually; chronic cardiomyopathy is found in approximately 30% of infected individuals.

Chagas Disease in Our Days

According to WHO and the World Bank, the incidence and social impact of Chagas disease have significantly decreased since the beginning of the 21st century, compared with previous decades. The driving factors behind this change are of a social nature

(urbanization, improved living standards, modernization of agriculture, and others), which complement specific interventions (vector and blood bank control, and better conditions for medical care). The new scenery of Chagas disease programs is replacing the classical vertical versus horizontal approach, because most of the countries are turning their public health systems toward a decentralized model. In the 1990s, globalization and market-controlled economies imposed the general tendency to deliver resources and responsibilities to the periphery, in order to improve small and efficient central and national structures. Considering the general conditions in endemic regions, transition to decentralization can be considered another new challenge, as low-income municipalities and countries tend to have a lack of sufficient expertise, organization, and political will to carry out the programs.

There are currently no major technical problems regarding the eradication of domestic triatomines: the results of various initiatives are considered successful in regions where they have been conducted meeting the minimum quality, coverage, and continuity requirements.

After a century since the description of the disease, Chagas still represents a major public health challenge in Latin America. In the last decades, several interventions encompassing the primary, secondary, and tertiary prevention levels of Chagas disease have been attempted. The control of both vector and blood transfusion-based transmission of *T. cruzi* (primary prevention) has been successful in many endemic regions, but early detection and etiological treatment of asymptomatic subjects have been largely underutilized.

Chagas Disease in the 21st Century: A Global Perspective

The worldwide picture of Chagas disease, particularly its incidence and morbidity, is indeed much better than it has been in the past years. Infections transmitted by vector and blood transfusions have significantly reduced in several countries, but new modes of transmission and disease spreading have been observed.

Vector control has been implemented in several endemic regions, but there is a lack of initiatives in others. *Triatoma infestans* was eliminated in large geographic areas but it remains the focus in the Chaco region. A similar situation exists in some Andean and Central American regions. Luckily, it appears that the Amazon region will not to be invaded and colonized by allochthonous species such as *T. infestans*, *T. brasiliensis*, *T. dimidiata*, and *Panstrongylus megistus*. At the same time, the encroaching of native species into human homes remains very rare in this region.

Levels of domestic infestation are not recovering to their former elevation in those areas where surveillance is maintained. Native wild species naturally remain, but their domestic density tends to decrease as control activities and surveillance are maintained.

Pyrethroid resistance has been detected in some situations, but has been addressed using alternative insecticides, such as carbamates. The existence of sylvatic *T. infestans* in some areas of the Southern Cone region requires attention. Progressive modernization of rural activities and living standards are contributing to the reduction of vector domiciliation.

The greatest challenges in vector control are without a doubt the dismantling of regular programs, mainly due to untimely decentralization. Because in several regions of Brazil, Venezuela, Central America, and Mexico, native secondary species such as *T. brasiliensis*, *T. maculata*, *T. dimidiata*, *T. pseudomaculata*, and *P. megistus* will remain in their natural habitats and may eventually invade human dwellings, a permanent surveillance system is necessary. Furthermore, the current trend in health care decentralization, which has underestimated Chagas disease a cause of mobility and mortality in endemic areas, may jeopardize the maintenance of vector control. Therefore, control programs in endemic areas should continue to receive priority at the local, national, and international levels. Regarding vector control, the 4 main challenges in the 21st century are: maintaining political interest and action, including allocating the necessary resources in those regions where the disease impact has decreased; objectively facing the irreversible tendency to centralization, maintaining the minimum central and regional reference structures to improve the efficacy and continuity of activities at the peripheral level; controlling secondary and ubiquitous species at the peri-domestic level; and maintaining a high and sustained level of community participation in order to ensure continuous epidemiological surveillance.

Almost all blood banks are being controlled in endemic countries, and so it is anticipated that in the next 20 years, only exceptional cases of blood-based HCD transmission will occur. A similar trend is also anticipated for congenital transmission, because the incidence of *T. cruzi* infection has been decreased in current generations of women in endemic areas.

The prevalence of Chagas disease is expected to decrease progressively in the next 3 decades, including a reduction in both incidence and mortality. Morbidity has also been decreasing due to improved medical care and the specific treatment in chronic individuals. At this point, the next step is the tremendous challenge of using a universal, specific treatment to manage the illness of the millions of individuals with Chagas disease.

There is a crossroad regarding Chagas disease research, and tension is mounting due to opposing views among researchers, health authorities, and policy makers. We must remain realistic, remembering that throughout the history of Chagas disease the scientific community has been the principal protagonist in disease management initiatives. Underestimating the possibility of resurgence of this “controlled” disease can be a fatal mistake, as was seen with resurgences of both tuberculosis and malaria. However, it is also true that many predicted epidemics ended up as false alarms.

Chagas Disease as a Neglected Tropical Disease in Latin America

Chagas disease is a neglected tropical disease (NTD) caused by *Trypanosomacruzi* infection. Around 13% of the Latin American population is considered at risk of this disease. The infection is endemic in 21 countries and affects 6-8 million individuals; it also produces 12.000 deaths worldwide per year. It was described by Carlos Chagas in 1909 during an outbreak in Brazil, Chagas disease has gained attention due to the “internationalization” of the disease. In the past, Chagas disease was an urban and periurban neglected tropical disease with a very close association with poverty. Chronic Chagas cardiomyopathy is the leading cause of nonischemic cardiomyopathy in Latin America and affects 20-40% of infected patients.

Chagas disease is a poverty disease; it affects population with low socioeconomic status. Problems controlling the spreading of this disease are related to the limitations related to the diagnosis, treatment and control. It is endemic in continental Latin America because it is transmitted through bites from the vector, especially at night. The vector defecates after sucking blood at night and the infection is transmitted through the parasite contaminated feces/urine through a break in the skin, mouth or eye. *T. cruzi* can also be transmitted through blood transfusions, organ transplantation, laboratory accidents, and vertical transmissions during childbirth.

The prevalence of the disease has been decreasing in the past decades, mostly due to successful control of the vector and blood transfusions control in several Latin America countries. Programs to prevent the spread of the vector include: systematic use of residual insecticides, house improvements, home hygiene, blood donor screening and information, education and community awareness of the disease. There are almost 300.000 infected people in the United States alone. Vector elimination programs have successfully decreased the transmission of Chagas disease, but Bolivia remains the country with the highest prevalence of Chagas disease in the world.

Observational studies suggest that antitrypanosomal treatment may improve the prognosis and decrease progression in *T.cruzi*-infected individuals asymptomatic or with early signs of Chagas cardiomyopathy. This hypothesis was tested in the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial. The result of BENEFIT reinforce that cardiac structural damage is not reversible and access to advanced heart failure therapies like left ventricular assist devices, heart transplants, and implantable cardiac defibrillators is limited to communities that are not even able to get simple devices like pacemakers. Therefore, identifying biomarkers that are predictive of those at highest risk for fatal outcomes of Chagas cardiomyopathy (CCM) could allow limited resources to use in the people who most need it.

Clinical findings of advanced cardiomyopathy and congestive heart failure (New York Heart Association class III or IV, cardiothoracic ratio >0.50 on chest radiography, and specific electrocardiogram (EKG) findings including atrial fibrillation, multiple

premature ventricular complexes, ventricular conduction deficits, low voltage, and pathologic Q waves and low QRS voltages) are well known as predictors of mortality in Chagas disease. Other less consistently identified risk factors are old age and male sex. From all cardiac biomarkers, just B-type natriuretic peptide (BNP) had been shown to predict mortality in Chagas cardiomyopathy.

The clinical course of Chagas disease is divided in 2 phases, acute and chronic; the acute phase is usually asymptomatic, this is also the most common occurrence and, if the patient survives it, goes to the indeterminate stage that can last 30-40 years until the patient dies. Chagas disease is a cause of heart failure and it is an independent risk factor for stroke.

With the introduction of better anti-arrhythmic therapy, such as beta-blockers and devices, progressive heart failure has over passed sudden death as the leading cause of death in Chagas disease.

PATHOGENESIS OF CHAGAS CARDIOMYOPATHY

The pathogenesis of the disease involves a complex interaction of different processes, related to tissue damage due to parasite persistence, inflammation, autoimmunity, fibrosis, dysautonomia, and microvascular changes. After the acute, febrile phase, the *T. cruzi* parasites hides in target tissues (cardiac and digestive system muscles) and enters in the chronic phase, almost always without clinical manifestations. However, low grade inflammation persists during the chronic phase related to the persistence of the parasite nests.

Myocardial damage due to persistence of the parasite is considered the most important mechanism in the development of Chagas cardiomyopathy and it seems to be associated to extensive inflammation and fibrosis; clinical presentation of the cardiomyopathy is very diverse and it makes difficult to calculate mortality according to the clinical phases of the disease.

Molecular Mechanisms of Cardiac Electromechanical Remodeling during Chagas Disease

To date, no studies have been performed using human tissue to identify the molecular pathophysiology of chagasic cardiomyopathy. Most of our knowledge is derived from animal tissues.

One of the first studies that aimed the study of molecular mechanism to explain the depressed cardiac function demonstrated that serum obtained from chagasic patients

exerted a positive chronotropic effect on isolated rat atrium. These results indicate that a soluble compound is likely to produce an adrenergic effect is released and could explain the observed tachycardia in the group of patients. During the chronic stage of the disease, the presence of autoantibodies against beta1-adrenergic receptor is observed in heart tissue, suggesting a possible attempt to control an excessive adrenergic activity. At the same time, the presence of autoantibodies against muscarinic M2 receptors have been detected that may be the cause of failure in the adrenergic activity.

A dysfunctional balance between muscarinic and adrenergic cardiac receptors activity may originate changes in both heart rate and cardiac muscle contractility. Prolonged and excessive activation of the cardiac beta-adrenergic system is well known to lead to severe depreciation of cardiomyocyte function due to modification of several systems in cardiomyocytes, including intracellular calcium homeostasis and cardiomyocyte excitability.

Another study reported that heart muscle contraction is compromised during the chronic phase of experimental *T. cruzi* infection in mice and that responses to norepinephrine is reduced, indicating that cardiomyocytes are dysfunctional at this stage. The authors have a theory that the observed negative chronotropic effect occurs as a result of autoantibodies-mediated muscarinic receptor activation that provokes the synthesis of cGMP and nitric oxide (NO), contributing to attenuated cardiac function. It is important to note that reduced cardiomyocytes responsiveness to norepinephrine is also observed in heart failure due to another's clinical conditions.

Role of the Inflammatory Response in the Severity of the Myocarditis and Heart Contractility during Chagas Disease

Studies have demonstrated that cardiomyocytes function is disrupted during the acute and chronic phases of *T. cruzi* infection in experimental animals. They found that cellular contractility, measured as a fraction of cardiomyocyte shortening, exhibited a complex behavior. Changes in contractility activity were evaluated in ventricular and atrial myocytes during the acute phase. The time of half contraction and relaxation were lengthened, regardless the number of days after infection and the heart region evaluated. The maximal contraction and relaxation rates were significantly slower and these phenomena were correlated with the presence of circulating TNF during the course of infection. The presence of TNF has been constantly observed in histopathological studies of heart from subjects who had died of Chagas disease. In recent studies, it has been shown that an elevated number of cells producing INF-gamma or TNF is observed in autopsy samples from patients with Chagas disease and it was associated with the occurrence of heart malfunction. Humans with Chagas disease have increased levels of

circulating TNF. Modulation of inflammatory response may be a potential therapeutic target to treat chagasic cardiomyopathy.

One important consequence of chronic inflammation in the heart during Chagas disease is remodeling and damage of different proteins belonging to the contractile machinery. The disruption of cardiomyocyte structure would release contractile proteins, such as troponin I, into the serum. Troponin I levels are higher in chagasic patients with cardiomyopathy than in patients with the indeterminate form of Chagas disease or in unaffected patients.

In another set of patients, a highly sensitive assay was used to demonstrate that chagasic patients with the cardiac form of the disease have increased circulating levels of cardiac troponin T, which has been correlated with the severity of cardiomyopathy. Another study revealed that chagasic patients have altered levels of circulating proteins that are involved in the contractile apparatus. Other mechanisms such as Ca²⁺ re-uptake would be engaged in the alteration of the contractile machinery. Reduced Ca²⁺ re-uptake would lead to incomplete SR refilling, contributing to diminished cardiomyocyte contractile force, one of the hallmarks of Chagas disease. Infection with *T. cruzi* appears to profoundly alter the contractile apparatus of cardiomyocytes. Additional studies using human cardiac tissue are necessary to improve our understanding of Ca²⁺ cycle remodeling and the implications of this process in the mechanical remodeling observed in chagasic cardiomyopathy.

Cardiac Electric Remodeling during Chagas Disease

One of the first studies to demonstrate the putative molecular basis for the electrical disturbances observed in Chagas disease was published in 1992. Cultured rat neonatal cardiomyocytes infected with *T. cruzi* exhibited reduced junctional conductance when compared to uninfected heart cells. Immunocytochemical studies demonstrated that parasitic infection significantly reduced connexin 43 expressions at junction membrane regions. It was later demonstrated that human cardiac tissue from patients in the chronic phase of Chagas disease, the distribution and expression level of connexin 43 are altered. Cultured mouse cardiomyocytes also exhibited significantly reduced connexin 43 expression after chronic exposure to TGF- β , suggesting an important physiopathological role for this molecule.

Despite the perturbations in heart rhythm that occur during the time course of Chagas disease, the capacity of *T. cruzi* to directly modulate membrane electrical properties of infected cardiomyocytes was only demonstrated in 1993. In this study, it was shown that isolated cardiomyocytes from mice, cultured for 2 days with Y strain of *T. cruzi*, exhibited an increased firing rate and reduced action potential duration without marked changes in maximum diastolic potential or action potential amplitude. This study was the

first to support the direct involvement of *T. cruzi* in the modulation of the membrane electrical properties of cardiomyocytes. Similar findings were obtained using a dog model of *T. cruzi* infection. The authors demonstrated that epicardium-derived cardiomyocytes isolated from hearts during the acute phase of infection exhibited reduced transient outward K_p current (Ito), which led to the ablation of the notch in the action potential waveform, with no apparent reduction in the slower components of total K_p current. These changes were not observed during the chronic phase in this study. Electrical cardiac disturbances are more easily detected in dogs during the acute phase than during the chronic phase of the infection that may sometimes be assimilated to an indeterminate form of Chagas disease. In fact, experimental *T. cruzi* infection in dogs resemble the human disease where clear signs of the chronic phase of the disease, including mechanical and electrical remodeling, may not appear for several months or even years.

Another factor that may be important in understanding the discrepancies between different studies is the influence of the parasite strains that are able to induce distinct phenotypes in the host.

A follow-up study demonstrated that after 24 hours of maintaining epicardialcardiomyocytes in a noradrenaline-culture medium the Ito was rescued in a PKC-dependent manner. A gradient exists in human cardiac tissue and is attributed to Ito density. It is larger in the epicardium and diminishing towards the endocardium. This transmural current density gradient mediates the appearance of the action potential notch, which underlies the normal J wave in the electrocardiogram (ECG). The loss of the notch gradient (especially in the right ventricle) causes life-threatening arrhythmias in human patients (Brugada syndrome). In rare cases of Chagas disease, ST elevation is observed; this finding, however, is a hallmark of Brugada syndrome.

In a well-defined mouse model study of *T. cruzi* infection to perform a series of experiments examining clinical phenotypes and molecular changes the investigators used Colombian strain of *T. cruzi* identifying some important mechanisms involved in the genesis of electrical remodeling. They characterized different degrees of electrical conduction disturbances in the acute and chronic phases, including tachycardia, P-wave alternans and repolarization disorders associated with QRS waveform and QT interval. The results also demonstrated that most animals presented some degree of electrical disturbance during ECG analysis. A correlation was established between altered membrane repolarization observed in QT interval and the downregulation of Ito. Reduced Ito contributes to action potential prolongation and in a recent study these alterations were maintained during later stages of experimental *T. cruzi* infection.

During the time course of Chagas disease, distinct intracellular signaling pathways that downregulates the expression of the mRNA encoding the Kv4.3 ion channel, which are the molecular entity of Ito, are activated. When cardiomyocytes are chronically exposed to TNF, Kv4.3 expression is reduced due to the production of both NO and

superoxide anion. As significant levels of TNF in heart are detected during the chronic phase of infection, it is reasonable to postulate that this long-term exposure of cardiomyocytes to TNF leads to Ito reduction and increased action potential duration. Such phenomena would contribute to increased incidence of early after depolarization, a powerful substrate to precipitate cardiac arrhythmias. It is well-known that cardiac arrhythmia is one of the main causes of death in the chronic phase of Chagas disease. Therefore, a prolongation of action potential associated with altered Ca²⁺ cycling in cardiomyocytes could be an important substrate to generate arrhythmias in Chagas disease. These observations might constitute the basis for new therapeutic strategies. There is no experimental evidence that suggests alterations in Ito in cardiomyocytes from chagasic patients but parallels can be drawn between the alterations in Ito in cardiomyocytes from experimental models and cardiomyocytes from patients in the end stage of heart failure caused by other etiologies.

Some studies have shown increased levels of systemic TNF in patients with heart failure. Although TNF is an interesting candidate for causing action potential repolarization disorders during the development of Chagas disease, other substances are capable of triggering such disorders by downregulating Kv4.3 via the activation of NO and superoxide anion production. Among them are angiotensin II (Ang II), IFN- γ , endothelin-1 (ET-1), and IL1- β .

The level of all these molecules is increased during the chronic phase of Chagas disease in humans and experimental models of *T. cruzi* infection. However, several lines of evidence demonstrated a possible crosstalk between TNF and these substances. TNF was described to induce Angiotensin II-dependent cardiac fibrosis by signaling through TNFR1, which enhances the generation of monocytic fibroblast precursors in the heart. Using a model of endothelin-1(ET-1) induced oxidative stress in the heart it was demonstrated that ET-1 may induce oxidative stress in this tissue by increasing TNF concentration and reducing the ratio of reduced and oxidized glutathione (GSH/GSSG). Amiodarone is the first line of pharmacological therapy for arrhythmias during chronic Chagas disease, primarily ventricular tachycardia, and it is effective in approximately 90% of patients. The pharmacological effects of amiodarone are attributed to blockade of inward Na⁺ and Ca²⁺ currents as well as blockade of outward K⁺ currents. Thus, the question of how an enhanced block of outward K⁺ currents may be anti-arrhythmic in Chagas disease must be addressed. Two possible explanations exist for these apparently contradictory findings: (1) patients in the chronic phase of Chagas disease have no clear alterations in outward K⁺ currents and/or (2) amiodarone has another pharmacological effect in Chagas disease patients that is capable of reducing arrhythmogenesis. In addition, unexpected roles for amiodarone have been reported in the treatment of Chagas disease (trypanomicidal activity, inhibition of *T. cruzi* infection and recovery of infected cardiac tissue).

The Inflammatory Response in the Heart during the Chronic Phase as a Therapeutic Target for Chagas Disease: Paradigm of TNF

Based on the studies' results it could be said that chronic heart inflammation is the pivotal trigger for heart dysfunction (electrical and mechanical remodeling) during the transition from acute to chronic phase of Chagas disease. TNF may play a crucial role in the reduction of Kv4.3 expression and therefore cause a significant reduction of Ito density and a subsequent delay in action potential repolarization.

Chagasic patients presenting with the cardiac form of Chagas disease have increased levels of circulating and/or heart TNF compared to individuals in the asymptomatic/undetermined phase of the disease.

Anti-TNF Therapy in Chagas Cardiomyopathy

Anti-TNF therapy could benefit patients presenting chagasic cardiomyopathy. Inhibition of TNF effects can be achieved with a monoclonal antibody against circulating TNF, such as infliximab, or with a soluble TNF receptor fusion protein such as etanercept. Etanercept is a recombinant soluble receptor TNF-R2-IgG1, whereas infliximab is a chimeric monoclonal antibody.

Blockage of TNF activity by infliximab directly or indirectly affects TNF mRNA expression during *T. cruzi* infection was associated with reduced tissue damage along with reduced myocarditis severity, without induction of parasite reactivation. Although significantly reduced in infliximab-treated mice compared to saline-injected ones, TNF mRNA expression was not abolished in the heart tissue during *T. cruzi* infection. This residual TNF production may contribute to the control of parasite growth indicating that the complete abrogation of TNF production or activity may not be required for the beneficial effect of TNF-based therapy on chagasic cardiomyopathy and may even be harmful in *T. Cruzi* infection. More recently, in patients with a chronic inflammatory condition, TNF neutralization was shown to downregulate IL-17, a cytokine upregulated in patients with chagasic cardiomyopathy. This highlights another indirect beneficial effect of anti-TNF therapy. While infliximab and etanercept both neutralize the soluble form of TNF, infliximab seems to have a more powerful pharmacologic effect than Etanercept. Transmembrane TNF is a precursor of the soluble form of TNF expressed on activated macrophages and lymphocytes as well as other cell types that exerts various biological functions that will contribute to modulation of local inflammation in a cell-to-cell contact manner as well as in a cell-type specific fashion. Therefore, transmembrane TNF plays a critical role in local inflammation and specifically in heart dysfunction. But the binding and neutralizing activities against soluble TNF are the most critical and common mechanisms of action of the anti-TNF agents.

Other anti-TNF therapeutic strategies may include the blocking of TNF receptors, TNFRp55 being responsible for most of the biological functions of TNF. It was surprising to find exacerbation rather than decreased inflammation after infection of TNFRp55/ mice with *T. cruzi*, a feature not related to an increased number of amastigote nests. The blockade of TNF receptor by specific compounds may not be the better strategy during *T. cruzi* infection due to the effect of membrane TNF and crosstalk of circulating form of TNF with other cytokine pathways. Although, it is possible to reason that TNF plays a complex role during Chagas disease. TNF is involved in the mediation of cardiac tissue damage but it also contributes to prolonging cell survival as reported by different authors.

The events resulting in immune-suppression contribute to Chagas disease reactivation episodes after heart transplantation, supporting the idea that *T. cruzi* is persistent and needs to be constantly controlled by host immune response. It is clear that more studies should be conducted to better establish the risk of anti-TNF therapy prior to performing trials in human patients.

CLINICAL MANIFESTATIONS OF CHAGAS DISEASE

Acute Phase

It is most frequent in children and occurs 7 to 10 days of parasite inoculation and can last 6 to 8 weeks. The acute phase diagnose is made in only 1-2% of infected patients. The main symptoms are fever and malaise. The main physical exam findings are hepatosplenomegaly and signs of meningoencephalitis and heart failure, secondary to acute myocarditis. Only 8% of vectoral transmissions present with signs of parasite inoculation, called Chagoma. The most common sign is eyelid edema or Romana's sign. However, this phase is commonly asymptomatic.

During the acute phase, the body has a high level of parasitemia which is detectable on laboratory tests (serologic tests for *T. cruzi* infections are often negative). Other nonspecific laboratory findings include leukocytosis with pronounced lymphocytosis, increased erythrocyte sedimentation rate, and abnormal liver function tests. Differential diagnosis is broad and includes other infectious etiologies like dengue, hepatitis, Hantavirus infection, and severe leptospirosis. Acute Chagas myocarditis has similar clinical presentation to other etiologies of myocarditis and the specific diagnosis can be made demonstrating the parasite in the biopsy.

Chronic Indeterminate Form

The chronic phase starts with an indeterminate form because the parasite is hidden in the tissue. There are different forms of clinical manifestations like cardiomyopathy with and without ventricular dysfunction. A barium enema test is not required in patients in this stage without constipation.

There are no formal protocols to follow up this stage, but electrocardiogram every year and chest X ray every 3 years is reasonable, because 2 to 5% of patients evolve to symptomatic disease every year.

Chronic Determinate Forms

Patients with Chagas disease that develop clinical signs and symptoms are divided in 3 groups: cardiac, digestive and cardiodigestive forms. The cardiac form of Chagas disease can present with or without ventricular failure.

After 5 to 30 years, 20 to 40% of patients with the indeterminate form will develop chronic Chagas cardiomyopathy and an additional 15% will develop chronic gastrointestinal disease.

The cardiac form can present with or without ventricular dysfunction. Chronic infection is confirmed with serologic tests and detection of immunoglobulin IgG anti-T. cruzi antibodies.

Symptoms include those associated to heart failure (dyspnea on exertion, fatigue and edema), arrhythmias (palpitations, dizziness, weakness, and syncope), tromboembolism (systemic and pulmonary), and chest pain syndrome (angina). Biventricular failure is often the first clinical manifestation, but also stroke or cardiac arrhythmia, including sudden cardiac death can also occur. Physical examination demonstrates a loud holosystolic murmur of mitral and/or tricuspid regurgitation, wide splitting of the second heart sound due to right bundle branch block. Examination findings of right ventricular failure are more pronounced than left ventricular failure.

Chest radiograph usually shows cardiomegaly with or without pulmonary congestion pattern. The most common electrocardiographic findings are right bundle branch block and/or left anterior fascicular block. Left ventricular apical aneurysm is common, whereas right ventricular aneurysm is much less common. Ventricular mural thrombi form in the dilated cardiac chambers, particularly in left ventricular apical aneurysm, can cause systemic emboli. Mural thrombi are equally frequent in the left and right chambers, but death is more common by emboli in the pulmonary circulation that can come from venous or right heart thrombi. Apical aneurysm can also be seen in hypertrophic cardiomyopathy.

Chronic Cardiomyopathy

Primary *T. cruzi* infection is acquired most commonly during childhood and young adulthood through vector transmission in endemic areas. The acute phase of Chagas disease is associated with local tissue inflammation at the parasite entry site and symptoms similar to others type of myocarditis, including malaise, fever, hepatomegaly and splenomegaly. The acute phase is associated with death in 5% of cases secondary to acute myocarditis, pericardial effusion, and/or meningoencephalitis. The electrocardiogram (ECG) in the acute phase can show sinus tachycardia, low voltage of the QRS complex, prolongation of the PR and/or QT intervals, and changes in ventricular repolarization. Ventricular arrhythmias, atrial fibrillation, and right bundle branch block can also develop and are associated with a worse prognosis. After the acute phase of the infection, most patients enter into the chronic phase.

Cardiac Involvement

Cardiac involvement is the most frequent and serious manifestation of chronic Chagas disease. Chagasic cardiomyopathy is a chronic myocarditis that affects all chambers of the heart, the parasympathetic cardiac nerves, and all levels of the conduction system. The pathogenesis of cardiac damage is complex and not completely understood. A least 4 possible mechanisms have been suggested: cardiac parasympathetic neuronal depopulation, immune-mediated myocardial injury, parasite persistence in cardiac tissue with secondary antigenic stimulation, and coronary microvascular abnormalities causing myocardial ischemia.

Cardiac Parasympathetic Neuronal Depopulation

This occurs during acute phase of the infection related to direct neuronal parasitism, as well as degeneration caused by periganglionic inflammation and an antineuronal autoimmune reaction. Cardiac parasympathetic neuronal depopulation has also been associated with abnormal cardiac autonomic heart rate regulation, suggesting that patients with Chagas disease have loss of inhibition of the parasympathetic tone in the sinus node. This imbalance in chagasic patients could in the long time lead to catecholamine-induced cardiomyopathy. There is need of more basic science investigation to correlate morphological and functional changes of the Chagas cardiomyopathy with cardiac parasympathetic neuronal depopulation.

Immune-Mediated Myocardial Injury

After parasitemia, tissue parasitosis and intense myocarditis (in the acute phase) are controlled by immune mechanisms. Mild, focal inflammation persists during the indeterminate form of Chagas disease. This process is composed mainly of mononuclear cells and it is associated with immunoglobulin and complement deposition in myocardial tissue. One of the mechanism linking cardiac inflammatory lesions and immune response in Chagas disease is autoimmune injury to cardiac structures. In addition, cross-reactive antibodies between human cardiac myosin heavy chain and the *T. cruzi* protein B13 are more frequently found in the sera from chagasic patients with manifestations of cardiomyopathy than in patients with the indeterminate form of the disease.

Parasite Persistence in Cardiac Tissue with Secondary Antigenic Stimulation

Some studies have shown that reduction or enhancement of parasite load is related to attenuation or exacerbation of cardiomyopathy, suggesting that persistence of the parasite is important in the pathogenesis of chagasic cardiomyopathy. Moreover, reactivation of the infection after years of the indeterminate form in patients with virally acquired immune deficiency syndromes supports this theory.

Coronary Microvascular Abnormalities

Pathological and clinical evidence suggest an important role of myocardial ischemia in the pathogenesis of chagasic cardiomyopathy. Several necroscopic studies have reported abnormalities of the microcirculation causing myocardial ischemia, which is responsible for the focal diffuse myocytolysis and subsequent reparative interstitial fibrosis characteristically found in chagasic hearts. Severe and diffuse arteriolar dilatation associated with microvessel tortuosity has been found in chagasic cardiomyopathy but not in normal hearts or those with idiopathic dilated cardiomyopathy.

Histopathology of Chronic Chagasic Cardiomyopathy

Chronic chagasic cardiomyopathy is characterized by a focal, diffuse inflammatory process composed of lymphomononuclear cells that produce myocytolysis, severe reparative fibrosis encasing individual or groups with myocardial fibers, and dilated microvessels with thin and fibrotic walls. Endomyocardial biopsies have reported higher

percentages of severe inflammation and fibrosis in patients with heart failure compared with indeterminate forms, suggesting a progressive character of the disease.

The inflammatory process and subsequent reparative fibrosis affects multiple areas of the myocardium, which explains the segmental motion wall abnormalities most frequently reported in the posterior lateral and apical LV. This condition predisposes patients to dilated cardiomyopathy and heart failure as well as the formation of ventricular aneurysms.

ROLE OF IMAGING STUDIES IN CHAGAS CARDIOMYOPATHY

The most useful initial imaging modality in suspected or confirmed Chagas disease is echocardiography because its sensitivity and low cost. Abnormalities of structures and function on echocardiography may be observed in both symptomatic and asymptomatic patients with Chagas disease. Early evidence of cardiac involvement may manifest as 1 or more areas of abnormal wall motion with preserved global systolic function. More severe forms of the disease are characterized by global dysfunction with or without the presence of the presence of ventricular aneurysms. Left ventricular apical aneurysm has been reported to occur in approximately half of the patients with moderate to severe cardiac impairment but also may be present in up to 9% of asymptomatic patients. Segmental wall motion abnormalities can occur everywhere but it is more common in the inferolateral wall.

ROLE OF CARDIAC BIOMARKERS IN CHAGAS CARDIOMYOPATHY

Advanced Chagas cardiomyopathy is associated with a very high short-term mortality. Both heart failure and sudden cardiac death are known to be causes of death in patients with chagasic cardiomyopathy. The highest rate of mortality are found to be in patients in stage D of heart failure, the most severe stage of cardiomyopathy based on left ventricular dilatation and ejection fraction. Stage D T-cruzi infected individuals experienced 40% mortality over 14 months.

BNP and NT-proBNP were identified as strong predictors of mortality. These markers are some of the most well characterized markers used to guide treatment and predict outcomes in heart failure. In heart failure from all etiologies, BNP-guided therapy reduces all cause mortality. Serum BNP levels were positively correlated with 5-year mortality in elderly adults. In individuals with Chagas cardiomyopathy, even in the absence of systolic dysfunction, had higher BNP levels than healthy control subjects did. For those with heart failure due to Chagas cardiomyopathy, BNP has previously been

shown to be a strong predictor of mortality. NT-proBNP levels are correlated with severity on left ventricular dysfunction in Chagas disease. NT-proBNP may be a better predictor of mortality than BNP, possible because of the longer half-life of NT-proBNP versus BNP.

It may be an association between MMP-2 levels to predict mortality in our study patients, suggesting that activation of the cardiac remodeling process is associated with negative outcomes in severe cardiomyopathy. This finding is consistent with studies of heart failure from other etiologies as well. In heart failure, MMP-2 messenger RNA expression and blood protein levels are increased. A high level of MMP-2 is a marker of diastolic heart failure and predicts poor outcomes. Higher levels of MMP-2 and MMP-9 correlate with more severe Chagas heart disease. Among patients with heart failure and high BNP levels, MMP-2 was the best predictor of mortality rather than BNP alone.

Chagasic Ventricular Arrhythmia

Ventricular arrhythmias are very common in Chagas disease and may present as atypical chest pain, dyspnea, palpitations, syncope, or sudden cardiac death. The prevalence and severity of chagasic ventricular arrhythmias correlates with the severity of the cardiomyopathy but can occur in patients with preserved LVEF.

Frequent monomorphic or polymorphic premature ventricular contractions are commonly seen on Holter monitoring in Chagas disease. Nonsustained VT is higher in prevalence comparing to other cardiomyopathies.

SUDDEN CARDIAC DEATH IN CHAGAS DISEASE

Sudden cardiac death is the most common cause of death in Chagas disease (55%-65%), followed by congestive heart failure in 25%-30% and cerebral or pulmonary embolism in 10%-15%. Most SCD cases occur in patients with manifest chagasic cardiomyopathy between 30 to 50 years old. 20% of patients that died suddenly do not report previous symptoms. SCD in chagasic patients is generally related to arrhythmias, and less common to thromboembolic events (massive pulmonary or cerebral embolism) or rarely a rupture of a LV aneurysm. Ventricular fibrillation has been reported to be the major cause of death of SCD. The risk of sudden cardiac death is not the same in all patients with chronic Chagas disease and this is why several authors have tried to identify predictor factors. A scoring system would be essential for establishing effective prevention strategies.

Identification of Chagasic Population at Risk

SCD in Chagasic disease is a catastrophic event that usually occurs in young and productive patients. It mostly occurs in patients with previous manifestations of cardiomyopathy but also it can occur in asymptomatic patients without evidence of LV dysfunction. Because of the wide range of presentations that it is not the same in every patient and identifying factors that increase risk becomes important. Prediction factors associated to SCD in chagasic cardiomyopathy include ventricular dysfunction and heart failure, nonsustained and sustained ventricular arrhythmias, severe bradyarrhythmias, syncope and previous cardiac arrest. The presence of NSVT on Holter monitoring has an important role in the identification of chagasic patients at risk of death. The highest risk of NSVT as a predictor of mortality is when it is combined with LV dysfunction. Rassi and colleagues developed identified six independent prognostic factors: NYHA class III or IV (5 points), segmental or global wall motion abnormality on echocardiogram (3 points), low QRS voltage (2 points) and male sex (2 points). This study NSVT on Holter monitoring was associated with an increased mortality risk of 2-fold and when it is combined with LV dysfunction increased to 15-fold. This scores classifies chagasic patients into 3 groups: low (0-6 points), intermediate (7-11 points), and high risk (12-20 points), with 10-year mortality of 10%, 44% and 84%, respectively. The overall mortality was 3.9% per year, and the rate of sudden cardiac death was 2.4% per year. The score is based in noninvasive clinical variables that are easy to use and inexpensive and it also identifies chagasic patients with increased risk who would need a more aggressive therapeutic approach.

Sustained VT has been associated with increased risk for SCD in Chagas disease. At 8-year follow-up in chagasic patients with sustained VT, mortality has been reported at 93% with more than 70% of the deaths occurring in the first 2 years and 90% occurring suddenly. The value of sustained VT as a predictor of increased risk for SCD is also supported by the results from analyses of the significance of sustained VT induced by programmed ventricular stimulation (PVS) during electrophysiologic studies in patients with Chagas disease.

Campos and colleagues in their study evidenced that the clinical course of Chagas disease vary significantly. The disease usually progress to chronic Chagas cardiomyopathy and this is the first cause of sudden death. The study was meant to develop a specific score for sudden cardiac death associated to Chagas disease. This score for overall death and did not consider cause of death. The main causes of death in chronic Chagascardiomyopathy are sudden death, refractory heart failure and stroke. Each complication is associated with has a specific predictor and different forms of prevention. Patients with heart failure should go for heart transplantation; patients at risk from suffering stroke should receive anticoagulation therapy; patients at risk of sudden cardiac death should get a cardio-defibrillator implant. In the study, the risk of death from sudden

cardiac death was associated to four predictor factors: long QT interval, severe left ventricular dysfunction, syncope and ventricular premature beats. The risk score has three subgroups of patients that can suffer sudden cardiac death (low, medium, high). The rates of sudden cardiac death in the 5.5 years period that the study lasted were 1.5%, 2.5% and 51%, respectively. The patients identified as high-risk of death can get a benefit from aggressive therapy, including electrophysiological studies using an implantable cardioverter.

Information Derived from Secondary Prevention Implantable Cardioverter-Defibrillator Observational Studies in Chagas Disease

Cardinalli-Neto and colleagues reported about 90 consecutive chagasic patients with aborted SCD or hemodynamically unstable VT whom got ICD implantation. All patients received Amiodarone before the index event, and after device implantation they were followed for a mean of 25 months. The age of patients was between 50 and 70 years old at implantation and the mean of LVEF was between 34% and 60%. 28% of the patients did not have LV dysfunction.

Primary Prevention of Sudden Cardiac Death in Chagas Disease: The CHAGASICS Study (Amiodarone against ICD Therapy in Chagas Cardiomyopathy for Primary Prevention of Death)

This study was aimed to assess whether the ICD also has the protective effect for primary prevention in chronic Chagas cardiomyopathy. The primary endpoint of this study was all-cause death, and enrollment will continue until 256 patients have reached this endpoint. Key secondary endpoints include cardiovascular death, sudden cardiac death, hospitalization for heart failure, and quality of life. Patients will be followed for 3 to 6 years, and data analysis will be done on an intention-to-treat basis. This is the first large-scale trial to assess the benefit of ICD therapy for primary prevention of death in patients with chronic Chagas cardiomyopathy and nonsustained ventricular tachycardia, who have moderate to high risk of death. The trial started in October 2014 and its estimated completion date is October 2019.

DIAGNOSIS OF CHAGAS DISEASE IN A NUTSHELL

The diagnosis of acute Chagas disease is made by the detection of the parasite in blood samples or by seroconversion. Enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence (IFF), indirect hemagglutination (IHA) test, and parasite polymerase chain reaction (PCR) are the most widely available tests. There are also rapid diagnostic tests that can directly detect *T. cruzi*.

TREATMENT OF CHAGAS CARDIOMYOPATHY

Pharmacology Treatment

Observational studies suggest that antitrypanosomal treatment may improve the prognosis and decrease progression of *T. cruzi*-infected individuals asymptomatic or with early signs of Chagas cardiomyopathy. This hypothesis was tested in the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial. The result of this trial reinforces that cardiac damage due to Chagas disease is not reversible, and access to advanced heart failure devices, heart transplants, and implantable cardiac defibrillators is limited to the communities that cannot afford simple devices as pacemakers.

The evidence supporting the use of antiarrhythmic drugs to prevent sudden cardiac death in Chagas disease is low. Current guidelines in Chagas disease establish that antiarrhythmics treatment is not required in asymptomatic chagasic patients with frequent isolated or repetitive PVCs when the LVEF is preserved. In patients with Chagas disease and LV dysfunction and frequent PCVs/nonsustained VT, the guidelines recommend amiodarone as the only drug available. There are no clinical trials supporting the role for amiodarone to reduce the risk for sudden cardiac death and total mortality in this context. Moreover, the use of amiodarone for the prevention of sudden cardiac death in dilated cardiomyopathy has shown a modest reduction in the risk of sudden cardiac death, with no reduction in all-cause mortality and increased risk for pulmonary and thyroid side effects. Amiodarone has also been used empirically to prevent the recurrence of sustained VT in patients with Chagas disease. Scanavacca and colleagues showed in an study that amiodarone seems to have a limited efficacy to prevent sustained VT recurrence in patients with Chagas disease, especially in patients with LV dysfunction and significantly reduced functional class.

The cornerstone of medical therapy is the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II-receptor blocker (ARB), beta blockers, and diuretics. All patients with Chagas cardiomyopathy should start ACE inhibitors or ARB, no matter their NYHA stage. For NYHA stage III or IV patients, spironolactone or eplerenone is

indicated, because studies have shown a reduction in morbidity as well mortality with these drugs.

Once the rennin-angiotensin-aldosterone system has been blocked, clinicians must start beta-blockers, which are also proven to be safe. In small study, association of enalapril, spironolactone and carvedilol showed improvement in several markers of cardiac function. For those with left-ventricular ejection fraction (LVEF) <45%, investigators noticed an increased in the LVEF.

Current guidelines indicate that the use of digoxin and diuretics are to improve symptoms after maximal titration of medical therapy with ACE inhibitor or ARB, blockage of aldosterone and beta-blockers, these agents have not shown to be effective in reducing mortality in previous studies of patients with heart failure.

A patient with medical therapy failure, heart transplantation is indicated. Even though Chagas cardiomyopathy has a bad prognosis, the outcomes get better with heart transplantation.

Pharmacologic treatment to prevent thromboembolism should follow the current guidelines on anticoagulation. The widespread use of antiarrhythmics to prevent ventricular arrhythmias is generally not indicated.

New Treatment Development

Several clinical studies have shown that Chagas disease pathogenesis goes beyond the parasite persistence per se; it is characterized by an inflammatory disease coupled with imbalanced immune disease. Therefore, the disease has been considered incurable and specific antiparasitic treatment has been neglected. Recent studies demonstrated clear correlation between the inflammatory process and the presence of the parasite. Because of relatively lower efficacy with benznidazole or nifurtimox, alternative drug design, development, or testing for new indications is warranted. *T. cruzi* is completely dependent on the endogenous produced sterols that are vital for the parasite membranes, cell division, growth, and development process. Therefore, the idea of screening the existing antifungal agents as a potential drugs for specific etiological treatment of Chagas disease was very attractive due to long previous clinical utilization in general practice and better safety profile as compared with currently approved benznidazole or nifurtimox. Those antifungal drugs act by blocking ergosterol synthesis in fungi via inhibition of the cytochrome P450 enzyme, called sterol 14 alpha-demethylase (CYP51). Research on clinical antifungal drugs for Chagas disease would be the most cost-efficient way to provide an immediate treatment, and among the azole approved for clinical systemic use, posaconazole has been exclusively studied as a potential new drug to treat chagasic patients with high *in vivo* activity against the infection caused by multiple, including several nitroderivative-resistance strains of *T. cruzi*.

Indications for Implantable Cardioverter-Defibrillator Implantation in Chagas Disease

The available studies suggest that patients with Chagas disease that got an ICD for secondary prevention tend to have higher LVEF, higher burden of life-threatening ventricular arrhythmia, higher incidence of appropriate ICD therapies, lower survival free from device therapy or death, and higher rate of all cause mortality.

ICD therapy for secondary prevention has been associated with a significant reduction in the risk of sudden cardiac death in Chagas disease. However, the impact of ICD implantation in all causes of mortality in secondary prevention in chagasic patients has shown contradictory results. Some studies have reported a very high mortality in chagasic patients that got ICD implantation even though a significant portion of them had a normal LVEF and functional class. Pump failure has been reported as the main cause of death and the number of device shocks was the strongest predictor of all-cause death.

The use of implanted cardioverter defibrillators (ICDs) for primary prevention in patients with ejection fraction <35% has never been tested in patients with Chagas disease and it is not recommended in the actual guidelines. Lack of resources in Latin America makes impossible to study the benefit of primary prevention with ICDs. There is evidence to use ICDs in secondary prevention in patients with sustained VT or were resuscitated from sudden cardiac death, or with syncope due to inducible VT.

Catheter Ablation of Sustained Ventricular Tachycardia in Chagasic Cardiomyopathy

The most common mechanism of sustained VT in chagasic cardiomyopathy is scar-related reentry. Scar is found in the inferolateral LV in more than 70% of patients. The reentry circuit responsible for scar-related VT may be subendocardial, subepicardial, or intramyocardial. Scars commonly are located inside the myocardium.

Epicardial Ablation of Sustained Ventricular Tachycardia in Chagas Heart Disease

Experts documented that epicardial access is necessary in greater than or equal to 20% of patients undergoing VT ablation in tertiary centers and especially in patients with nonischemic cardiomyopathies.

Entering the pericardial space involves use of Tuohy needle, which is curved at one end, making it ideal for penetrating pericardial membranes. The risk of pericardial

bleeding is 10% with this technique, although most of the bleedings are minor and transient. Severe bleeding requiring surgical repair occurs in only in less than 2% of the patients. Pericardial adhesions are frequently seen in patients with a history or prior ablation. The electrograms obtained during epicardial mapping are similar to those seen during endocardial mapping both in patients with chagasic cardiomyopathy and in other patients with other forms of cardiomyopathy. Use of irrigated-tip catheter may provide deeper injury resulting in more effective ablation. However, this may increase the risk of damage of the coronary arteries or extracardiac structures. Patients with recurrence ICD shocks despite antiarrhythmic therapy can achieve short term and medium term benefits with catheter ablation.

Clinical Course After CDI Implantation in Chagas Cardiomyopathy

Evidence about the efficacy of implantable cardioverter-defibrillator (ICD) to CSD prevention originates from large trials of secondary prevention and primary prevention. Those studies show the superiority of ICD over drugs, especially in ischemic and idiopathic cardiomyopathies. Data about the efficacy of ICD in patients with CCC are controversial. There is evidence from two registries and two retrospective studies of secondary prevention. The Brazilian Cardiac Implantable Electronic Devices Guideline makes no specific mention of the indication of ICD in patients with CCC.

Prospective and retrospective studies assessing the clinical course of patients with CCC and ICD are scarce. Moreira and colleagues developed a study that was aimed to compare the clinical course after ICD implantation of patients with Chronic Chagas Cardiomyopathy (CCC) and ischemic heart disease (IHD), and at assessing the survival and event-free survival curves (appropriate shocks, appropriate therapies and death).

Sudden death due to malignant ventricular arrhythmia (VT or VF) is a well-known complication of Chagas cardiomyopathy. It occurs mainly between 30 years and 50 years of age, being rarer after the sixth decade of life, and predominates in the male sex. It usually occurs during routine activities, physical exertion or emotion, being instantaneous in half of the cases. In the other half, death is preceded by premonitory symptoms for seconds or, more rarely, minutes. Differently from IHD, whose sudden death frequency peaks in the morning, in CCC, deaths seem to predominate in the afternoon. Therapeutic strategy to avoid sudden death in IHD is well established. In CCC, however, it is a great challenge.

Moreira's study has a high number of CCC patients receiving appropriate ICD shock (36.5%) and appropriate therapy (42.9%), with a significant difference from that found in IHD patients ($p < 0.05$). Chronic Chagas cardiomyopathy increased 2.07 times the risk of receiving appropriate therapy [95% confidence interval (CI): 1.02-4.17]. That high percentage of appropriate shock and therapy triggered by ICD was similar to data of other studies, corroborating the concept relative to the severe arrhythmogenic nature of CCC,

which is an inflammatory pancarditis with right injury to the electric system and fibrosis, which feeds the reentry mechanism, which is the major responsible for the genesis of tachyarrhythmias. Barbosa and colleagues have shown an incidence of 62.7% of appropriate therapy in CCC patients and of 37.3% in non-chagasic patients during a median follow-up of 266 days, in addition to a 2.2-time increase in the risk of receiving appropriate therapy in CCC (95% CI: 1.2-4.3; $p < 0.05$). Martinelli and colleagues follow up 11 CCC patients and 42 patients with either ischemic or idiopathic heart diseases; they have shown a likelihood of fatal ventricular arrhythmia non-occurrence of 0% in chagasic patients and of 40% in non-chagasic patients, during a mean follow-up of 660 days. Other studies have reported follow-up of 20 CCC patients and 35 IHD patients submitted to ICD implantation, have reported 85% of chagasic patients receiving appropriate therapy as compared to 51% of the IHD group, during a mean follow-up of 180 days.

Mild left ventricular dysfunction was shown to predict appropriate therapy. It is worth noting that the patients receiving ICD with mild left ventricular dysfunction were those undergoing ICD due to secondary prevention of sudden death; it is well known that patients receiving ICD due to secondary prevention are at higher risk of repeating the arrhythmic event.

Ventricular dysfunction and functional class IV were predictors of mortality. Also, the incidence of appropriate shock and therapy in CCC patients was higher than that in IHD patients; mortality, however, was similar. No sudden death occurred during the follow-up of CCC patients receiving ICD, as well as no death related to the device implantation procedure. This suggests the efficacy and safety of ICD implantation in CCC.

There has not been a published large randomized clinical trial comparing the efficacy of ICD in CCC with that of active drug or placebo. Although Chagas disease was identified and described by the Brazilian researcher Carlos Justiniano Ribeiro Chagas more than 100 years ago, the best treatment for ventricular arrhythmias and sudden death prevention remain a challenge.

PROGNOSIS OF CHAGAS CARDIOMYOPATHY

Deaths are rare in the acute phase and most of them attributable to Chagas disease are due to cardiovascular complications. Sudden deaths accounts for approximately 55% to 65% of death in patients with chronic Chagas and it is likely to be underestimate due to underreporting, especially in rural areas. The main causes are VT of ventricular fibrillation, complete atrioventricular block, or asystole. Progressive heart failure accounts for 25% to 30% of deaths, and stroke in 10% to 15%:

Cucunuba et al. concluded in their work that Chagas disease is associated with statistically significant with a higher mortality; the relative risk was 1.74 and the

attributable risk percent was 42.5%. The higher mortality of Chagas disease patients is regardless the clinical presentation. Annual mortality increased with clinical severity. They suggest the use of NYHA grading system to classify the disease progression associated with *T. cruzi* infection. There are also rapid diagnostic tests that can directly detect the causative parasite, *T. cruzi*. In the chronic phase, the diagnostic often requires serologic testing with IgG anti-*T. cruzi* antibody testing. Making the diagnosis requires 2 positive laboratory tests and if one of the results is discordant, a third one is necessary to confirm the diagnosis. The definitive diagnosis of Chagas disease requires a serologic confirmation.

REFERENCES

- Araújo, Edgard Ferreira de, Eduardo Gregório Chamlian, Alexey Pomares Peroni, Wilson Lopes Pereira, Sylvio Matheus de Aquino Gandra, and Luiz Antonio Rivetti. 2014. "Terapia De Ressincronização Cardíaca Em Pacientes Com Cardiomiopatia Chagásica Crônica: Seguimento De Longo Prazo." *Brazilian Journal of Cardiovascular Surgery* 29: 31-36. ["Cardiac resynchronization therapy in patients with chronic Chagas cardiomyopathy: a long-term follow-up." *Brazilian Journal of Cardiovascular Surgery* 29: 31-36].
- Barbosa, Marco Paulo Tomaz, Andre Assis Lopes do Carmo, Manoel Otávio da Costa Rocha, and Antonio Luiz Pinho Ribeiro. 2015. "Ventricular Arrhythmias in Chagas Disease." *Revista da Sociedade Brasileira de Medicina Tropical* 48: 4-10.
- Barros, Márcio Vinícius Lins. 2015. "New Predictors of Malignant Ventricular Arrhythmias in Chagas Disease: Searching for the Holy Grail." *Revista da Sociedade Brasileira de Medicina Tropical* 48: 1-3.
- Benziger, Catherine Pastorius, Gabriel Assis Lopes do Carmo, and Antonio Luiz Pinho Ribeiro. 2017. "Chagas Cardiomyopathy." In: *Cardiology Clinics*, 31-47: Elsevier.
- Braggion-Santos, Maria Fernanda, Gustavo Jardim Volpe, Antonio Pazin-Filho, Benedito Carlos Maciel, José Antonio Marin-Neto, and André Schmidt. 2015. "Sudden Cardiac Death in Brazil: A Community-Based Autopsy Series (2006-2010)." *Arquivos Brasileiros de Cardiologia* 104: 120-27.
- Cruz, Jader Santos, Fabiana Simão Machado, Catherine Ropert, and Danilo Roman-Campos. 2017. "Molecular Mechanisms of Cardiac Electromechanical Remodeling During Chagas Disease: Role of Tnf and Tgf-beta." *Trends in Cardiovascular Medicine* 27, no. 2: 81-91.
- Cucunubá, Zulma M., Omolade Okuwoga, María-Gloria Basáñez, and Pierre Nouvellet. 2016. "Increased Mortality Attributed to Chagas Disease: A Systematic Review and Meta-Analysis." *Parasites and Vectors* 9, no. 1: 42.

- de Souza, Adriana Campos Junqueira, Gil Salles, Alejandro Marcel Hasslocher-Moreno, Andréa Silvestre de Sousa, Pedro Emmanuel Alvarenga Americano do Brasil, Roberto Magalhães Saraiva, and Sergio Salles Xavier. 2015. "Development of a Risk Score to Predict Sudden Death in Patients with Chaga's Heart Disease." *International Journal of Cardiology* 187: 700-04.
- Dias, João Carlos Pinto. 2015. "Evolution of Chagas Disease Screening Programs and Control Programs." *Global Heart* 10, no. 3: 193-202.
- Dubner, Sergio, Elina Valero, Ricardo Pesce, Jorge González Zuelgaray, José C. Pachon Mateos, Silas Galvao Filho, Walter Reyes, Raúl Garillo, and I. C. D. Labor Investigators. 2005. "A Latin American Registry of Implantable Cardioverter Defibrillators: The ICD-Labor Study." *Annals of Noninvasive Electrocardiology* 10, no. 4: 420-28.
- Gonzalez-Zuelgaray, Jorge, Oscar Pellizon, Claudio A Muratore, Elsa Silva Oropeza, Rafael Rabinovich, José Luis Ramos, Maria Cristina Tentori et al. 2013. "Lack of Current Implantable Cardioverter Defibrillator Guidelines Application for Primary Prevention of Sudden Cardiac Death in Latin American Patients with Heart Failure: A Cross-Sectional Study." *Europace* 15, no. 2: 236-42.
- Healy, Chris, Juan F. Viles-Gonzalez, Luis C. Sáenz, Mariana Soto, Juan D. Ramírez, and Andred' Avila. 2015. "Arrhythmias in Chagasic Cardiomyopathy." *Cardiac Electrophysiology Clinics* 7, no. 2: 251-68.
- Mensah, George A., Kristin M. Burns, Emmanuel K. Peprah, Uchechukwu K. A. Sampson, and Michael M. Engelgau. 2015. "Opportunities and Challenges in Chronic Chagas Cardiomyopathy." *Global Heart* 10, no. 3: 203-07.
- Oliveira, Gustavo Bernardes F., Álvaro Avezum, and Antônio José Cordeiro Mattos. 2015. "Perspectives in Chagas Disease Treatment." *Global Heart* 10, no. 3: 189-92.
- Pereira, Francisca Tatiana Moreira, Eduardo Arrais Rocha, Marcelo de Paula Martins Monteiro, Neiberg de Alcantara Lima, Carlos Roberto Martins Rodrigues Sobrinho, and Roberto da Justa Pires Neto. 2016. "Clinical Course after Cardioverter-Defibrillator Implantation: Chagasic versus Ischemic Patients." *Arquivos Brasileiros de Cardiologia* 107: 99-100.
- Sherbuk, J. E., E. E. Okamoto, M. A. Marks, E. Fortuny, E. H. Clark, and G. Galdos-Cardenas. 2015. "Biomarkers and Mortality in Severe Chagas Cardiomyopathy." *Glob. Heart* 10.
- Veloso, Henrique Horta. 2016. "Underutilization of Implantable Cardioverter-Defibrillator in Studies Proposing Risk Scores to Predict Death in Chagas Heart Disease: Just a Reflection of the Real World." *International Journal of Cardiology* 203: 1082-83.

Chapter 9

CARDIAC MAGNETIC RESONANCE FOR RISK STRATIFICATION OF SUDDEN CARDIAC DEATH

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ABSTRACT

Despite substantial therapeutic advances in the prevention and treatment of ICM and chronic HF, the burden of SCD remains a global health issue. In clinical practice the primary prevention of SCD is largely based on the identification of severe left ventricular systolic dysfunction by measurement of left ventricular ejection fraction in both ischemic or and non-ischemic heart disease. However, based on this criterion only 10% of primary prophylactic ICD implantations are delivering life-saving therapy, exposing the remaining 90% to all of the risks of ICD implantation and therapy without benefit. CMR is a non-invasive and radiation-free technique able to detect changes in biventricular volumes and function predictive of malignant ventricular arrhythmias and SCD. Of note, CMR offers the unique opportunity of myocardial tissue characterization and the advantage of accurate and reliable detection of arrhythmogenic morphological substrate in both ICM and NICM. LGE is a very established technique to image myocardial fibrosis and a robust predictor of adverse outcome in both ICM and NICM. Nowadays, a growing body of evidence demonstrates LGE imaging could substantially improve patient selection for ICD therapy by providing excellent visualization and

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characterization of the arrhythmic substrate. Further, the presence of myocardial edema on T2-weighted imaging has been associated with more advanced disease and increased arrhythmic burden in patients with hypertrophic cardiomyopathy. Finally, the development and validation of parametric mapping techniques for the quantification of myocardial edema and diffuse interstitial fibrosis will certainly help improve risk assessment of SCD in the next few years.

ABBREVIATIONS

ARVC/D	Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia
AL	Amyloid Light
AMI	Acute Myocardial Infarction
ATTR	Amyloid Transthyretin
CAD	Coronary Artery Disease
CMR	Cardiac Magnetic Resonance
CS	Cardiac Sarcoidosis
CV	Cardiovascular
DCM	Dilated Cardiomyopathy
ECV	Extracellular Volume
FWHM	Full-Width Half Max
LGE	Late Gadolinium Enhancement
HCM	Hypertrophic Cardiomyopathy
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
ICM	Ischemic Cardiomyopathy
IOC	Iron Overload Cardiomyopathy
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVEF	LV Ejection Fraction
MI	Myocardial Infarction
NICM	Non-Ischemic Cardiomyopathy
NYHA	New York Heart Association
PIZ	Peri-Infarct Zone
RV	Right Ventricle
RVEF	RV Ejection Fraction
SCD	Sudden Cardiac Death
STRM	Signal Threshold versus Reference Myocardium
TFC	Task Force Criteria
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

INTRODUCTION

CV diseases are responsible for approximately 17 million deaths every year in the world, approximately 25% of which are SCD, mostly due to arrhythmias, namely VT or VF (Priori et al. 2015). This amounts to a death toll of 1-1.5 per 1000 people per year in the industrialized world. Prediction of SCD fuelled one of the most active areas of investigation during last decades, but unfortunately only every third SCD victim can be identified by the markers for SCD risk that are currently known. Identification of other patient subgroups at high risk for SCD is crucial to save the remaining 0.6 per 1000 annual SCD victims in the population (Kirchhof, Breithardt, and Eckardt 2006). Although current guidelines do recommend prophylactic ICD in patients with LVEF < 35%, only one-third would receive an appropriate shock. Of note, more than 60% of SCD cases occur in individuals with LVEF > 35%. Hence, both sensitivity and specificity of LVEF for identifying patients at risk of SCD are limited. In this perspective efforts to improve cost-effectiveness of ICD implantation and identify a better risk-stratifying tool are quite desirable. Evidence suggests that the presence and extent of myocardial tissue heterogeneity with regions of scar and interstitial fibrosis provide a substrate for ventricular arrhythmias, that is believed to be the major cause of SCD in both ICM and NICM.

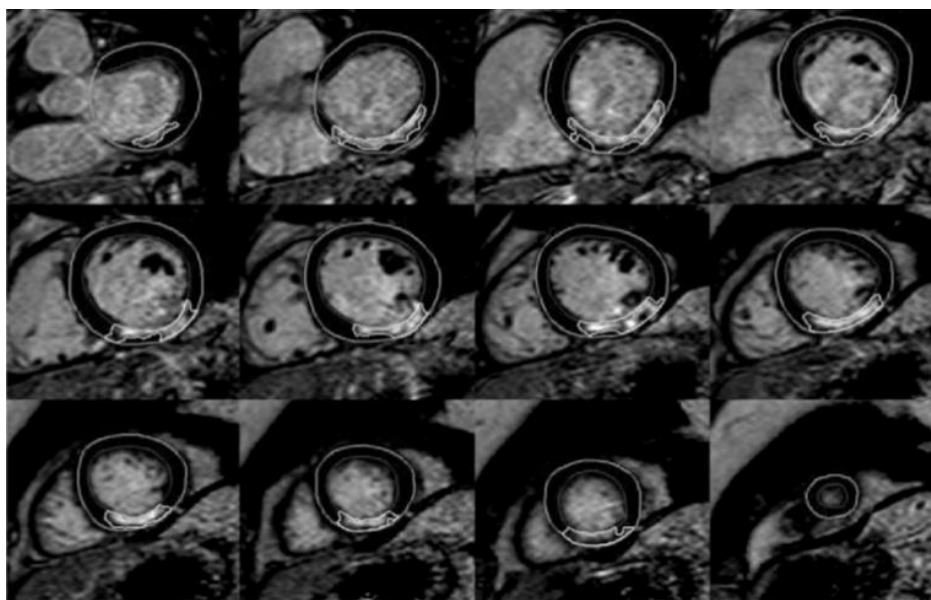


Figure 1. Patient LGE-imaging. Representative short axis (2D-phase sensitive inversion recovery) LGE-images in one patient with ischemic myocardial scarring from base to apex (advancing from left to right). The outer trace denotes the epicardial border and the inner trace denotes the endocardial border. The total LGE was carefully delineated within the myocardium. Reproduced with permission from Jablonowski et al.: Infarct quantification using 3D inversion recovery and 2D phase sensitive inversion recovery; validation in patients and ex vivo. *BMC Cardiovascular Disorders* 2013;13:110.

Of note, quantification of total scar burden by CMR (Figure 1) has been shown to be superior to LVEF in predicting VT/VF and appropriate ICD therapy in both ischemic and non-ischemic populations (Aljaroudi et al. 2013).

CMR is an established noninvasive imaging modality allowing tissue characterization and identification of the arrhythmogenic substrate through a bunch of pulse sequence techniques dedicated to the assessment of fibrosis (LGE imaging), edema (T2-weighted imaging) and fat (T1-weighted imaging), in combination with cine imaging, the gold standard for cardiac morphology and function.

In this chapter, we will summarize the growing body of literature about the clinical role and prognostic value of CMR in the identification of patients at high risk for SCD.

ISCHEMIC CARDIOMYOPATHY

Despite substantial advances in both prevention and treatment of CV risk factors and ICM, CAD (Hill and Sheppard 2010) is by far the leading cause of SCD in adulthood (Priori et al. 2015, Myerburg, Kessler, and Castellanos 1992). Among individual with previous AMI risk of SCD is approximately 5-fold higher than in the general population (Zaman and Kovoov 2014).

ICD is the most effective prevention against SCD (Priori et al. 2015, Epstein et al. 2008). Since its introduction into clinical practice it has been shown to be cost-effective (Smith et al. 2013), more efficacious than antiarrhythmic drug therapy alone to improve long-term survival (Goldenberg et al. 2010), both in primary (Moss et al. 1996, Buxton et al. 1999, Moss et al. 2002, Bardy et al. 2005) and secondary (The AVID Investigators 1997, Connolly, Gent, et al. 2000, Kuck et al. 2000) prevention. However, the high number-needed-to-treat (Tung and Swerdlow 2009), the non-negligible rate of complications (Goldenberg et al. 2006) and the high cost (Weiss et al. 2002) call to redefine the best ICD candidates (Fishman et al. 2010), while we might still wonder whether we have cast the net of SCD prevention too widely (Tung and Swerdlow 2009).

Given the widespread availability of life-saving interventions for individuals at higher risk of arrhythmic death, the optimal SCD risk stratification strategy should ideally identify all patients who will develop a fatal ventricular arrhythmia and rule-out those who will not (Goldberger et al. 2008). CMR imaging stands out as one of the most promising tool with robust evidence supporting its use for the risk prediction of SCD among patients with ICM (Wu 2012).

CMR FOR RISK STRATIFICATION IN PRIMARY PREVENTION OF SCD

Currently, primary prevention of arrhythmic events is still largely based on the detection of severe left ventricular systolic dysfunction, as assessed in most cases by transthoracic echocardiography, with its inherent and well-known limitations (Dagres and Hindricks 2013). However, there is a general consensus on the need for a more effective risk stratification method besides LVEF to identify patients that would benefit the most from an ICD.

A number of clinical, laboratoristic and instrumental parameters have been taken into account for arrhythmic risk stratification purpose (Priori et al. 2015, Goldberger et al. 2008, Wellens et al. 2014, Zaman and Kovoov 2014). However, due to poor reproducibility and conflicting results (Scott, Rosengarten, Shahed, et al. 2013), their use is not currently recommended in clinical practice (Priori et al. 2015, Goldberger et al. 2008).

Criteria of ICD implantation for primary prevention of SCD derive from several randomized controlled trials (Moss et al. 1996, Bardy et al. 2005, Moss et al. 2002, Buxton et al. 1999) and meta-analyses (Nanthakumar et al. 2004, Ezekowitz, Armstrong, and McAlister 2003) and include the documentation of LVEF $\leq 35\%$ in combination with NYHA class II-III, or LVEF $\leq 30\%$ and NYHA class I, at least 40 days after AMI (Priori et al. 2015, Epstein et al. 2008).

However, although associated with high risk of SCD in patients with ICM, LVEF does not account for the vulnerable substrate expressed by structural heart disease, thus providing only an indirect measure of the arrhythmic potential (Klem et al. 2012).

LVEF showed both low sensitivity and specificity (Buxton et al. 2010). Accordingly, up to 70% of SCD do occur in individuals with LVEF $>35\%$ (Stecker et al. 2006) (Gorgels et al. 2003, Solomon et al. 2005, Makikallio et al. 2005). Moreover, patients with reduced LVEF but without further SCD risk factors have lower risk of SCD compared with patients with LVEF $>30\%$ but with additional risk factors (Klem et al. 2012, Buxton et al. 2007). Notably, improvement of therapeutic strategies, such as early and complete myocardial revascularization, optimization of antithrombotic and antiarrhythmic drug therapy and cardiac resynchronization therapy, has been continuously lowering the incidence of ventricular arrhythmias in patients with low LVEF (Huikuri et al. 2009). Hence, an increasing number of patients undergoing ICD implantation based on current international guidelines recommendations will never benefit from device therapies, but will be exposed only to peri- and post-procedural complications (Greenberg et al. 2004, Moss et al. 2004, Kirkfeldt et al. 2014).

Goldenberg et al. explored the importance of adequate SCD risk stratification in a post-hoc analysis of the Multicenter Automatic Defibrillator Implantation Trial II

(Goldenberg et al. 2008) and reported a lack of ICD survival benefit among patients at both higher and lower risk (U-shaped curve), so that only a minority of patients undergoing ICD implantation did receive effective therapies (Tung, Zimetbaum, and Josephson 2008).

These findings call for the development of more effective multi-parameter SCD risk stratification models. Among the emerging imaging modalities proposed for the study of structural heart diseases, CMR plays an important role for ICM diagnosis (Kim et al. 2016, Hundley et al. 2010), diagnostic and prognostic evaluation of SCD survivors (White et al. 2012, Neilan et al. 2015) and families of SCD victims (Priori et al. 2015). CMR allows distinction between acute and chronic ICM through the assessment of myocardial edema by T2-weighted sequences, the identification of reactive interstitial fibrosis by T1-mapping analysis and ECV calculation (Burt et al. 2014), and the evaluation of the infarcted area (replacement fibrosis) by LGE imaging (Figure 2) (Kim et al. 1999, Wu et al. 2001, Kwong et al. 2006, Schelbert et al. 2012).

Among different LGE patterns, the presence of a subendocardial or transmural LGE fitting a coronary distribution is strongly suggestive of ischemic scar (Flett et al. 2011).

Several studies reported greater predictive accuracy of prognostic models in which LGE evaluation was included in addition to LVEF in both post-infarct (Roes et al. 2007, Kelle et al. 2009) and stable coronary artery disease populations (Catalano et al. 2012).

The pro-arrhythmic role of ischemic scar was confirmed both by histological and in-vivo studies documenting a positive correlation between scar burden and ventricular arrhythmias susceptibility (Bolick et al. 1986, de Bakker et al. 1988).

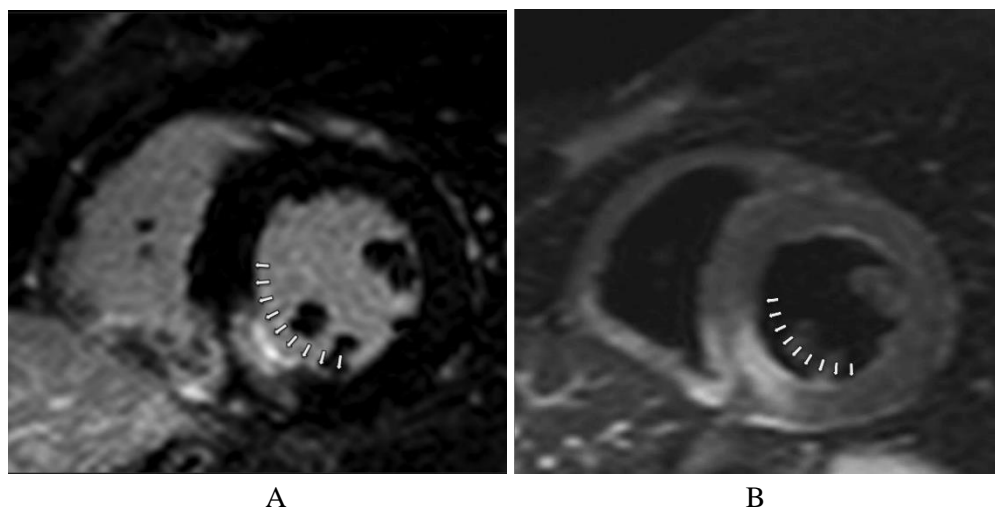


Figure 2. Ischemic cardiomyopathy. A) Late gadolinium enhancement imaging. The arrows indicate the transmural LGE distribution. B) T2-weighted sequences. Arrows indicate edema of the inferior wall, inferior septum and the inferior wall of the right ventricle.

By different LGE analysis techniques, the total infarct zone can be selectively segmented into two different areas: the infarct core and the PIZ. The latter seems to be a dynamic and heterogeneous interface between myocytes and collagen representing the organic substrate for prominent anisotropy, electrical leakage, changes in refractoriness and slowing or conduction blocks (Zipes and Wellens 1998, Crawford et al. 2010, Takahashi et al. 2004). Its remodeling seems to reduce drastically after 30 days from the index event (Schuleri et al. 2012). These features make the PIZ a highly arrhythmogenic substrate. This hypothesis was tested in a small study (Perez-David et al. 2011) of patients with monomorphic VT that showed correspondence between LGE areas of damaged myocardium with conduction skills and slow conduction areas at three-dimensional endocardial mapping. In almost half of the population, LGE areas turned out to be a critical isthmus for arrhythmia development.

Different criteria have been reported in the literature to differentiate the infarct core from PIZ (Flett et al. 2011, Mavrogeni et al. 2013, Heydari and Kwong 2014), including the signal intensity of LGE over the remote myocardium (threshold of 2 and 3 SD) (Yan et al. 2006) and the maximum recorded intensity (the FWHM method) (Schmidt et al. 2007, Roes et al. 2009, Zeidan-Shwiri et al. 2011), sometimes obtained with manual visual methods, but in most cases using semi-automated dedicated software.

Observational studies identified the extent of LGE as a strong predictor of major adverse CV events (de Haan et al. 2011).

In a study of 48 patients with heart failure and ICM referred for electrophysiological study, Bello et al. reported that a scar burden $\geq 26\%$ of LV mass was highly predictive of inducible arrhythmias (Bello et al. 2005). In a large observational study (Kwon et al. 2009) enrolling 349 patients with ischemic heart failure, the extent of LGE transmural extent was associated with higher all-cause mortality or need for heart transplantation over 2.6 years of follow-up (Kwon et al. 2009). Scott et al. reported similar results in 64 ICD recipients with ICM undergoing LGE imaging: both percent infarct size (hazard ratio per 10%, 1.75; 95% CI, 1.09 to 2.81; $P = 0.02$) and number of transmural scar segments (hazard ratio per segment, 1.40; 95% CI, 1.15 to 1.70; $P = 0.001$) were indeed associated with appropriate ICD interventions in multivariable analysis (Scott et al. 2011).

Furthermore, transmural extent of LGE normalized to the total size of the scar (relative infarct transmural extent) was an independent predictor of appropriate ICD interventions and CV death in patients implanted in primary prevention (Boye et al. 2011). Notably, a relative infarct transmural extent threshold of 43% yielded 88% sensitivity and 90% negative predictive value for the aforementioned composite outcome.

In another study of 177 medically treated patients with chronic ICM undergoing low-dose dobutamine stress CMR, segmental LGE extension (scar spatial extent ≥ 6 segments) rather than LGE transmural extent predicted higher rate of major adverse CV events (Kelle et al. 2009). Unexpectedly, in patients with extensive scar burden the presence of contractile reserve was associated with poorer outcome. This evidence would confirm

that revascularization of hibernating myocardium may prevent incident ischemic events or ventricular arrhythmias (Schinkel et al. 2006).

Klem et al. reported that a total scar burden $\geq 5\%$ of myocardial mass was an independent predictor for death and appropriate ICD intervention (HR 4.6, 95% CI 1.8 - 11.8; $p = 0.002$) in patients with both ICM and NICM after 2 years of follow-up (Klem et al. 2012). Authors also found that: i) LVEF was not an independent predictor of the primary endpoint at multivariate analysis; ii) the primary endpoint occurred similarly in the two subgroups of patients with LVEF $< 30\%$, but total scar extension $< 5\%$, and with LVEF $> 30\%$; iii) patients with LVEF $> 30\%$ and total scar burden $> 5\%$ had a similar risk of adverse outcomes compared with the subgroup of patients with LVEF $< 30\%$.

In a prospective study by Gao et al., where LGE imaging was classically performed 10 to 15 minutes after intravenous gadolinium contrast administration using standard two-dimensional segmented inversion recovery gradient echo pulse sequence, and STRM and FWHM techniques were used and compared for myocardial hyper-enhancement quantification, the presence of total hyper enhanced mass ≥ 2 SD by STRM and $> 50\%$ by FWHM was associated with the highest risk (HR per 10 g: 1.70; 95%CI 1.26–2.30 and HR per 10 g: 95%CI 1.09–3.02, respectively) of appropriate ICD intervention, resuscitated sudden cardiac arrest or SCD (Gao et al. 2012).

A number of studies aimed to explore the incremental prognostic value of myocardial scar quantification highlighted the importance of gray zones (regions of intermediate contrast enhancement likely representing potentially arrhythmogenic zones of viable and non-viable myocardium), which have been found to be independently associated with increased risk of VT inducibility, appropriate ICD intervention and mortality (Lee and Goldberger 2013).

In a series of 167 consecutive patients with ICM who were found to have abnormal LGE, the extent of PIZ (as defined by a signal-intensity threshold between 2 to 3 SDs above a reference remote myocardial region) provided incremental prognostic value beyond left ventricular systolic volume index or LVEF and was independently associated with a 40% increased risk of CV and all-cause mortality (Yan et al. 2006).

Schmidt et al. by using a simplified versions of the FWHM method for the quantification of tissue heterogeneity found that PIZ extension, but neither total infarct size, nor reduced LVEF, predicted VT inducibility at programmed ventricular stimulation (Schmidt et al. 2007).

In a cohort of 91 primary prevention ICD recipients, Roes et al. could observe that: i) infarct gray zone extension was the strongest independent predictor of appropriate ICD intervention; ii) infarct gray zone extension below the median of 16.7 g yielded a 95% negative predictive value for the prediction of appropriate ICD therapy (Roes et al. 2009).

Finally, in a cohort of 55 patients with ICM undergoing primary prevention ICD implantation, de Haan et al. analyzed the extent of scar core size and PIZ based on three previously validated LGE analysis techniques and evaluated their ability to predict

ventricular arrhythmias (de Haan et al. 2011). Regardless of the methodology, quantification of total scar size was a strong predictor of ventricular arrhythmias at 2-year follow-up. However, in this series any distinction between infarct core and PIZ did not improve the diagnostic accuracy of total scar size alone.

A meta-analysis of 11 observational studies, pooling a total of 1105 patients and 207 arrhythmic events (SCD, resuscitated cardiac arrest, ventricular arrhythmias, appropriate ICD therapy), confirmed the strong relationship between scar extent and risk of incident ventricular arrhythmic events in patients with reduced LVEF (Scott, Rosengarten, Curzen, et al. 2013).

All these data strongly support the incremental prognostic value of scar imaging for the prediction of SCD, advocating CMR as an indispensable tool to refine clinical decision-making for the prevention of SCD in patients with ICM. Nevertheless, it remains to be proven whether LGE can be used to select patients who are likely to derive most benefit from ICD therapy, a question that needs to be answered by prospective randomized data.

RISK STRATIFICATION FOR PRIMARY PREVENTION OF SCD IN THE EARLY PHASE AFTER AMI

Patients with ICM are exposed to a considerable higher risk of SCD compared with age- and sex-matched general population, with an estimated incidence of 1.4% per month in the first 30 days decreasing to 0.14% per month after two years from the index event (Solomon et al. 2005). The use of ICD for primary prevention of SCD in the early phase after AMI was evaluated in two large randomized controlled clinical trials, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) (Hohnloser et al. 2004) and Immediate Risk-Stratification Improves Survival trial (IRIS) (Steinbeck et al. 2009). Despite the presence of severe left ventricular systolic dysfunction and the evidence of impaired cardiac autonomic function, ICD implantation during the first 30–40 days after AMI failed to establish any survival benefit in both studies. Notably, the observed reduction in the rate of arrhythmic death in the ICD arm was paralleled by the increase in the rate of non-arrhythmic cardiac death. Such observations support a fundamental paradigm that claims that “the patients at highest risk of receiving appropriate therapy (who might most “need” the ICD) are the ones at highest risk of dying of non-arrhythmic causes soon after the therapy, likely offsetting the potential benefit from the ICD therapy; those at lowest risk of non-arrhythmic death (in whom the device can “do the most good”) are the ones at much lower risk of ever receiving appropriate therapy in the first instance” (Dorian et al. 2010).

Based on autopsy results of VALIANT (Pouleur et al. 2010) and Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL) (Dickstein, Kjekshus, and Group 2002), it has been observed that 30-day AMI mortality was essentially linked to mechanical complications or reinfarction.

The results of these studies highlight the current unavailability of effective tools discerning the arrhythmic risk profile from the generic risk of death in this timeframe.

As a consequence, ICD implantation in the first six weeks after AMI or at the time of surgical revascularization (Bigger 1997) is generally not recommended (Priori et al. 2015, Kusumoto et al. 2014).

Larose et al. examined 103 STEMI patients with LGE-CMR and T1- and T2-weighted sequences within 12 hours from revascularization and after 6 months. LGE volume was the best long-term predictor of left ventricular dysfunction in multivariable analysis at a median follow-up of 2.6 years (Larose et al. 2010). Furthermore, in the acute phase LGE extension $\geq 23\%$ yielded 89% sensitivity and 74% specificity in predicting left ventricular dysfunction at 6 months and was associated with a significant increased risk of CV morbidity and mortality (HR 1.72; 95%CI 1.43-2.00).

Izquierdo et al. evaluated 440 STEMI patients with CMR within 7 days from the index event and reported that both LVEF $< 36\%$ and infarct size $> 31\%$ were independent predictors of arrhythmic events at a median follow-up of 30 months (Izquierdo et al. 2013).

A substantial proportion of patients with AMI undergoing primary percutaneous coronary intervention develop chronic cardiac failure owing to poor restoration of microvascular function and myocardial perfusion, despite restoration of epicardial vessel patency. This occurrence is called the “no-reflow” phenomenon, which is secondary to microvascular obstruction, irreversible microvascular injury and subsequent intramyocardial hemorrhage. The use of LGE shows a hypoenhanced core within a hyperenhanced region that is often also referred to as microvascular obstruction (Figure 3) (Betgem et al. 2015). Use of a T2-weighted sequence shows intramyocardial hemorrhage (because of paramagnetic effects elicited by hemoglobin breakdown products) indicating severe microvascular injury. Both microvascular obstruction and intramyocardial hemorrhage as assessed by CMR have been associated with increased risk major adverse cardiac events and CV death and may serve as future markers for SCD risk stratification in ICM patients.

In summary, although not currently recommended by international guidelines, there is a growing body of evidence supporting the role of CMR in the prognostic stratification of patients with ICM, already in the early phase of AMI, with potentially game-changing implications for prevention of SCD.

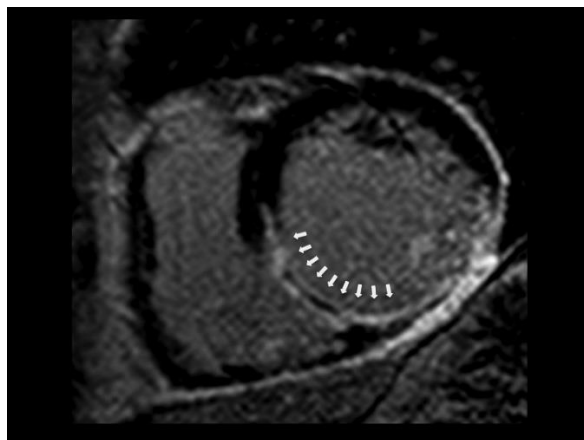


Figure 3. The “dark rim” within the hyper enhancement (arrows) of the inferior septum is referred to as microvascular obstruction at late gadolinium enhancement imaging.

RISK STRATIFICATION FOR SECONDARY PREVENTION OF SCD

SCD survivors represent a very high-risk population for recurrence of arrhythmic events (van Welsenes et al. 2011). Three pivotal trials (The AVID Investigators 1997, Connolly, Gent, et al. 2000, Kuck et al. 2000) and a meta-analysis (Connolly, Hallstrom, et al. 2000) documented a significant reduction in all-cause mortality and SCD with ICD on top of optimal medical therapy compared with optimal medical therapy alone. Therefore, ICD implantation is a class I recommendation after any cardiac arrest without reversible causes occurring >48h after index MI in both American and European guidelines (Epstein et al. 2008, Priori et al. 2015).

Two studies examined CMR applications beyond recommended diagnostic tests among candidates to ICD implantation for secondary prevention against SCD and sustained monomorphic VT.

White et al. proved that CMR examination has diagnostic utility for the detection of myocardial substrate in patients with malignant ventricular arrhythmia, particularly unsuspected acute injury, incremental to that provided by routinely ordered non-CMR imaging, leading to a reclassification of diagnosis category in half of the patients (White et al. 2012).

In a cohort of 137 SCD survivors (without known ICM and/or any myocardial revascularization) CMR detected a potential arrhythmic substrate in 76%, and identified LGE in 71% of patients. In most cases it was unrecognized MI (Neilan et al. 2015). Notably, at multivariable analysis presence and extent of LGE were the strongest predictors of incident major adverse cardiac events.

Results of these studies do certainly confirm the utility of CMR for refining diagnosis and risk stratification among SCD survivors.

GAPS IN EVIDENCE AND FUTURE PERSPECTIVES

Reduced LVEF is the main criteria underlying current indications for ICD implantation for primary prevention of SCD. However, any strategy for primary prevention based on LVEF alone has major limitations.

LGE is a well-established technique, offering better discriminative accuracy of LGE than LVEF for individual arrhythmic risk stratification and a possible game-changing solution to two major unmet clinical needs:

- a) the identification of those subjects within the ICM population with an indication to primary prevention ICD implantation but at low risk of SCD, that would not benefit from the device, and would only be exposed to possible complications weighing unnecessarily on health care costs;
- b) the identification of individuals at high-risk of SCD among those patients that does not meet primary prevention ICD implantation criteria, but still represent the vast majority of patients who die suddenly after a MI.

Nonetheless, a number of important issues does limit routine clinical use of CMR for risk stratification of SCD. First, much of the evidence supporting LGE imaging relies upon small, single-center, observational studies. Accordingly, the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) (Kadish et al. 2009) trials was conceived and aimed to test whether patients with an infarct size $\geq 10\%$ of LV mass and with a range of ejection fractions, randomized to ICD plus appropriate medical therapy would have improved survival compared with patients randomized to medical therapy alone. Unfortunately, the trial has been prematurely halted due to poor enrollment.

Second, there exists a lack of agreement on what method yields greater reliability and reproducibility in the evaluation of ischemic scar. In addition, there is conflicting evidence with regard to which type of scar (i.e., total scar, core-infarct or PIZ) and what scar extension (absolute or relative) and degree of transmuralty are most predictive of events according to LGE analysis absolute or relative total infarct size extension.

Third, besides LGE imaging other CMR applications are emerging with great potential to show their incremental prognostic value. Accordingly, For example, assessment of myocardial area at risk assessment by native T1-mapping in the early stage of an acute coronary syndrome has been shown to predict functional recovery after revascularization (Dall'Armellina et al. 2012). Furthermore, ECV, as assessed by native and post-contrast T1 mapping, was an independent predictor of regional and global LV functional recovery, adding incremental prognostic value over LGE in the setting of reperfused AMI.

For all such reasons, current evidence on the use of LGE imaging and other emerging CMR applications requires adequate validation in large, multi-center, randomized controlled trials.

The Cardiac Magnetic Resonance GUIDEd Management of Mild-moderate Left Ventricular Systolic Dysfunction CMR-GUIDE (NCT01918215) is an ongoing controlled trial actively randomizing patients with mild-moderate LV systolic dysfunction (LVEF 36-50%) and ventricular scar on CMR to either ICD or implantable loop recorder insertion. Primary outcome measure would be the occurrence of SCD or VT leading to syncope. The results are eagerly awaited.

NON-ISCHEMIC CARDIOMYOPATHIES

Dilated Cardiomyopathy

DCM is currently defined by the presence of LV or biventricular dilatation and systolic dysfunction in the absence of abnormal loading conditions (i.e., hypertension, valve disease) or CAD sufficient to cause global systolic impairment.

DCM is a leading cause of HF and heart transplantation in the western world (Rakar et al. 1997, Codd et al. 1989). Almost half of cases are genetically determined with an autosomal pattern of inheritance (Taylor et al. 2003). Inflammatory etiologies can be also frequently observed. Of note, progression of myocarditis to DCM has been documented in 20% of cases and is pathogenically linked to chronic inflammation and viral persistence. Myocarditis presenting as acute decompensated heart failure is associated with very poor prognosis (Elliott et al. 2010, Watkins, Ashrafian, and McKenna 2008). An important issue related to DCM deals with reversible etiologies, as alcoholic, peripartum and tachycardia-induced cardiomyopathies (Pinto et al. 2016). Beyond the most common causes of DCM – i.e., CAD and hypertension – AC, the advanced hypokinetic stage of HCM, amyloidosis and hemochromatosis should be included in the differential diagnosis of DCM (Authors/Task Force et al. 2014, Rigato et al. 2013, Haugaa et al. 2017, Sen-Chowdhry, Syrris, and McKenna 2010, Pantazis and Elliott 2009).

Prognosis of individuals with DCM significantly improved during the last decades, though 50% of patients still die within 2 years from the diagnosis (Franciosa, Wilen, and Ziesche). Early diagnosis during the subclinical stage of the disease and family-based cascade screening programs contributed to improve survival of DCM patients (Aleksova et al. 2009, Moretti et al. 2010). Optimizing medical treatment through careful dosage titration is key to improve symptoms and reduce CV morbidity. Nonetheless, more than 30% of DCM patients fail to benefit from optimal medical treatment, likely because of

genetic factors (Zecchin, Merlo, and Pivetta 2012). In the absence of an accurate prognostic model, strict surveillance is the cornerstone of DCM management.

To date, the principal objectives of DCM therapy include treatment of HF and prevention of SCD. The leading cause of SCD in pediatric and adult DCM populations is due to malignant ventricular arrhythmias (Maron et al. 2006, Pinto et al. 2016). ICD is known reduce the incidence of SCD (Codd et al.), but current stratification algorithms for prophylactic ICD therapy lack both sensitivity and specificity (Grimm, Christ, and Bach 2003). Indeed, SCD occurs in more than two-thirds of cases among individuals with LVEF>35%, and effective risk stratification protocols for the prevention of SCD in DCM are eventually far from being established.

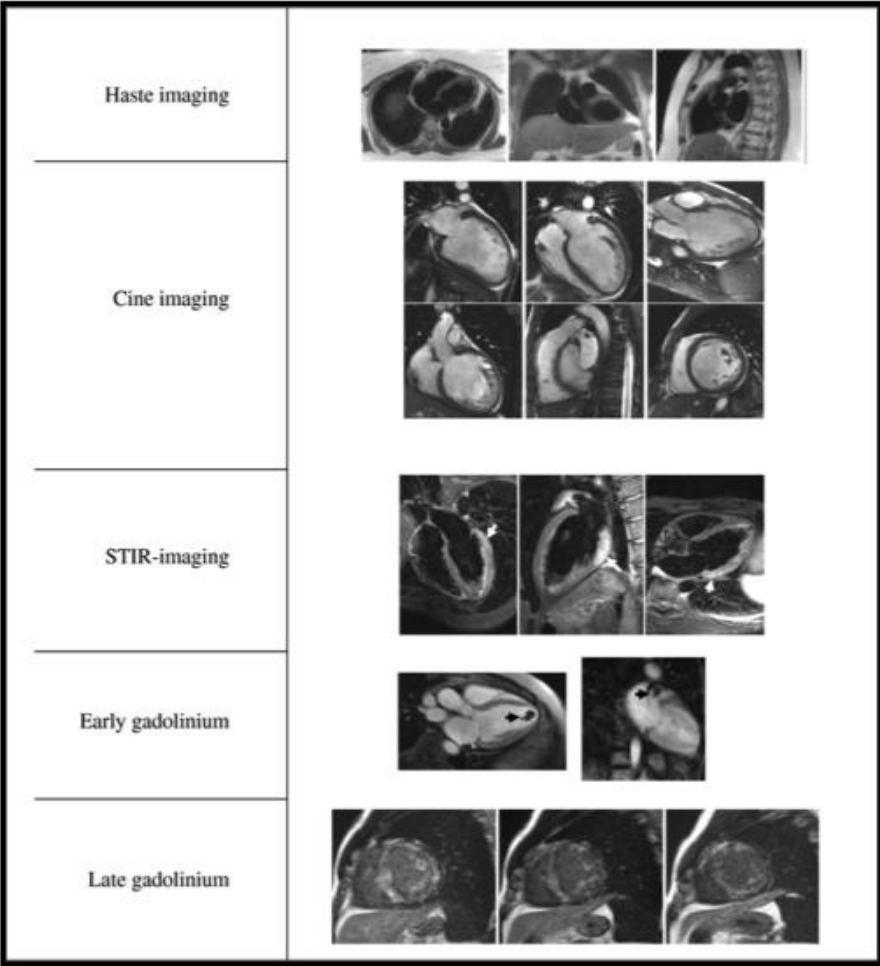


Figure 4. Standard cardiomyopathy protocol including HASTE, cine imaging, T2-weighted-imaging searching for inflammation/oedema (white arrows), early gadolinium imaging to detect thrombus (black arrow) and LGE to identify fibrosis or infiltration (diffuse LGE typical of amyloidosis). Reproduced with permission from Parsai et al.: Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. Journal of Cardiovascular Magnetic Resonance 2012;14:54.

In this setting, CMR may be a game-changer. CMR is currently used to explore multiple aspects in DCM. In a single 45–60 minute study (Figure 4), CMR can provide three-dimensional data on cardiac anatomy, function, tissue characterization, myocardial perfusion, valvular and hemodynamic function in any selected plane, regardless of patient's habitus and without ionizing radiation (Parsai et al. 2012). The etiology of DCM may be achieved by evaluating the patterns of myocardial fibrosis by LGE imaging. Accordingly, subendocardial or transmural LGE, especially when distributed in coronary perfusion territories, is pathognomonic of ICM (McCrohon, Moon, and Prasad 2003). Conversely, LGE is frequently absent in patients with DCM, though a typical mid-wall (intramural) LGE pattern can be found in up to 30% of idiopathic DCM cases (Figure 5). Of note, in a subgroup of patients with NICM a pseudo-ischemic pattern can be found (Mahrholdt et al. 2005). Finally, subepicardial LGE is pathognomonic of myocarditis (Mahrholdt et al. 2005).

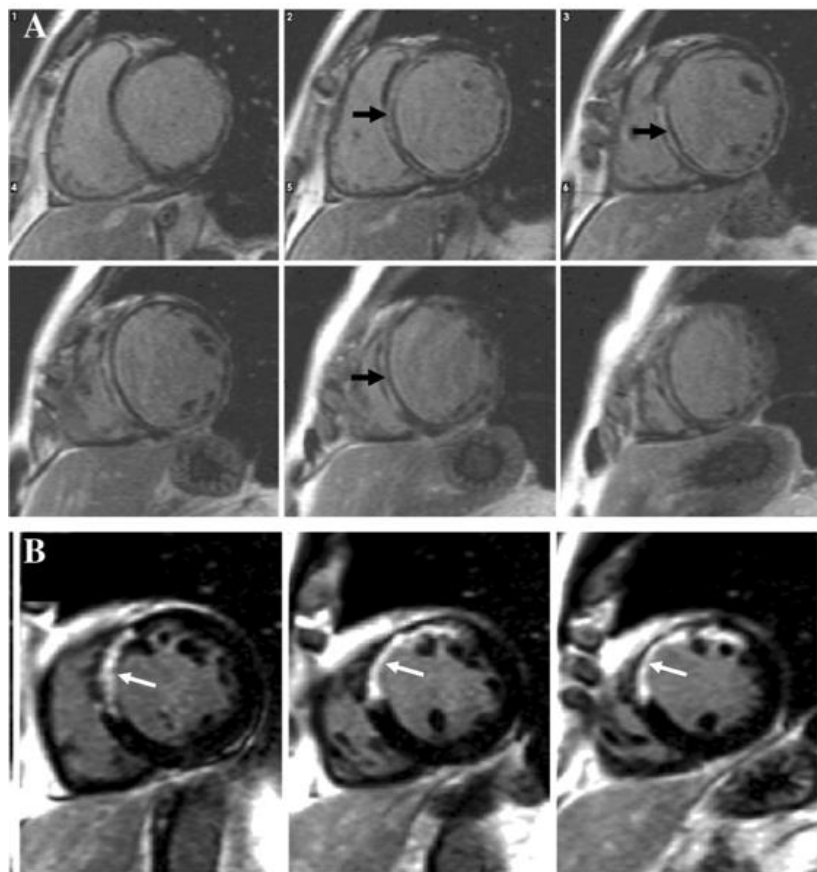


Figure 5. Pattern of fibrosis in DCM. Typical mid-wall LGE seen in DCM (A, arrows) differing from the sub-endocardial ischemic pattern (B). Reproduced with permission from Parsai et al.: Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. *Journal of Cardiovascular Magnetic Resonance* 2012;14:54.

A number of studies are available that specifically address the risk of SCD of patients with idiopathic DCM. Nazarian et al. found that patients with NICM and scar distribution involving 26% to 75% of LV wall thickness were more likely to have inducible VT, regardless of baseline LVEF, hence promoting scar imaging to identify i) the substrate for inducible VT; and ii) high-risk patients with NICM and mild or moderate LV dysfunction missed by current LVEF-based criteria (Nazarian, Bluemke, and Lardo 2005). Assomull et al. observed the presence of mid-wall fibrosis in 35% of 101 consecutive patients with non-ischemic DCM. Mid-wall LGE was associated with higher rate of all-cause of death and CV hospitalization, and resulted an independent predictor of SCD and/or sustained VT (Assomull, Prasad, and Lyne 2006). Further, in a prospective, longitudinal study aimed to assess of the prognostic value of LGE in a cohort of 472 consecutive patients with DCM, Gulati et al. found that both the presence and extent of mid-wall replacement fibrosis were associated with an increased likelihood of all-cause mortality (HR 2.43; 95%CI: 1.50-3.92), regardless of LVEF and other established prognostic factors (Gulati et al. 2013). Finally, a meta-analysis based on 2,948 patients enrolled in 29 observational studies, confirmed LGE as a robust predictor of ventricular arrhythmias or SCD across a wide spectrum of patients with DCM, highlighting the need for randomized controlled trials aimed to evaluate i) whether patients with DCM and LGE could benefit from a primary prevention ICD regardless of LVEF; ii) patients with DCM and severe left ventricular dysfunction, but without LGE, actually derive any survival benefit from primary prevention ICDs (Di Marco et al. 2016).

Hypertrophic Cardiomyopathy

HCM is a common inherited cardiomyopathy, occurring in approximately 1 in 500 individuals, and commonly diagnosed in young adults. HCM is defined by the presence of myocardial hypertrophy in the absence of abnormal loading conditions such as hypertension or aortic stenosis sufficient to cause the observed abnormality (Gersh, Maron, and Bonow 2011). HCM is diagnosed in the presence of an asymmetrically increased LV wall thickness >1.5 cm (>1.3 cm in familial forms).

The main pathophysiological features and clinical manifestations of HCM include LV diastolic dysfunction, dynamic LV outflow tract obstruction and HF. Marked LV hypertrophy, associated with increased ventricular wall stiffness due to interstitial fibrosis, is responsible for LV diastolic dysfunction (reduced compliance and abnormal relaxation). The unfavorable end-stage evolution (LV dilatation and systolic dysfunction) is morphologically indistinguishable from DCM. SCD is frequently the first clinical manifestation of HCM, occurring without warning signs or symptoms, and the most visible outcome of HCM in young people, including trained athletes participating in competitive activity, without significant difference between genders (Mandorla et al.

2010). ICDs are effective in preventing this life-threatening complication. On the other hand, antiarrhythmic pharmacologic therapy does not provide adequate protection from SCD (Maron and Maron 2013).

CMR helps in the diagnosis of HCM by identifying areas of hypertrophy not well visualized by echocardiography, providing accurate assessment of papillary muscles, perfusion abnormalities and wall thickness measurements, and differentiating HCM from its phenocopies (Codd et al., Nagueh et al. 2011, Reichek and Gupta 2008). CMR also provide the opportunity for in-vivo myocardial scar characterization by LGE imaging (Figure 6). Notably, extensive LGE (>15% LV mass) has been associated with increased risk of SCD, independent of other high-risk features.

Microvascular dysfunction and myocardial ischemia may be also present in HCM. Although normal at rest, during pharmacological hyperemia myocardial perfusion is usually significantly reduced in HCM patients compared with healthy controls (Petersen et al. 2007); additionally, a significant inverse relationship between coronary flow reserve extent of LV hypertrophy can be observed.

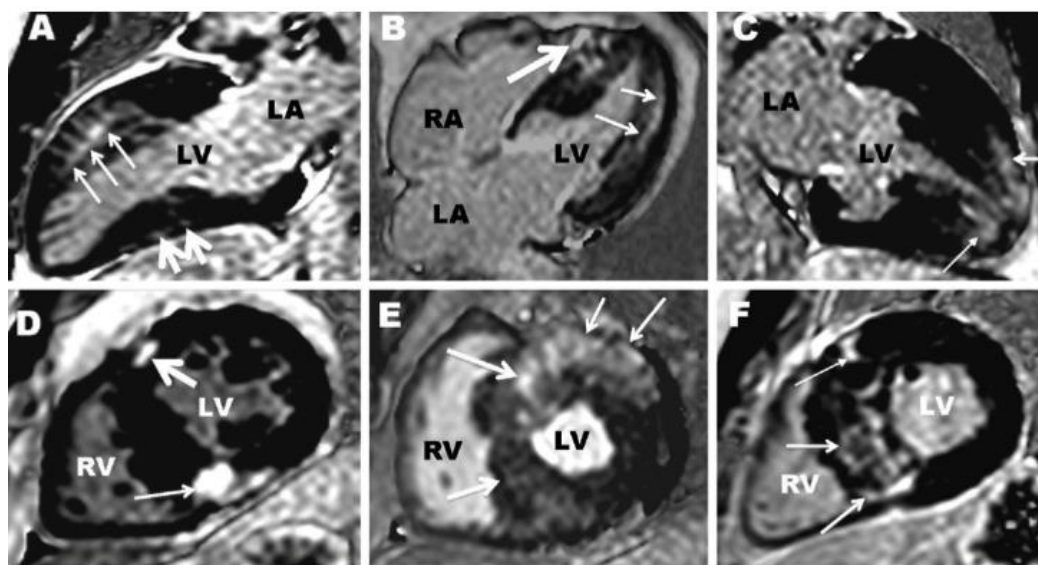


Figure 6. Contrast-enhanced CMR images in 6 different HCM patients demonstrating the diverse pattern and extent of late gadolinium enhancement in this disease. (A) extensive transmural LGE in the anterior wall (small arrows) with smaller focal area in the inferior wall (small arrows); (B) mid-myocardial LGE in the lateral wall (small arrows) and diffuse LGE in the ventricular septum which extends into the RV wall (large arrows) in a 26 year-old man with "end-stage" phase of HCM with an ejection fraction of 40%; (C) LGE confined to the LV apex (arrows); (D) LGE localized to the insertion area of the RV wall into the anterior (large arrow) and posterior ventricular septum (small arrow); (E) transmural LGE involving the majority of the ventricular septum (large arrow) and lateral wall (small arrow). (F) Basal short-axis image with transmural LGE located predominantly in the ventricular septum (arrows). RA= right atrium; RV= right ventricle; LA= left atrium; LV= left ventricle. Reproduced with permission from Maron et al.: Clinical Utility of Cardiovascular Magnetic Resonance in Hypertrophic Cardiomyopathy. *Journal of Cardiovascular Magnetic Resonance* 2012;14:13.

CMR plays also a major role in the screening of familiar forms of HCM, particularly when genetic analyses are non-contributory (Reant et al. 2015). In the absence of overt morphologic evidence of the disease, the presence of myocardial crypts, abnormal convexity of the interventricular septum into the LV, longer anterior mitral valve leaflet, abnormal apical trabeculae, as well as myocardial fibrosis and diastolic dysfunction on echocardiography may identify the subclinical HCM phenotype (Germans et al. 2010, Gersh, Maron, and Bonow 2011, Maron 2012). Consequently, the detection of a subclinical HCM phenotype preceding LV hypertrophy in relatives of probands may facilitate closer clinical surveillance. However, further studies are needed to explore i) whether preclinical signs of HCM in the absence of a known pathogenic genetic mutation precede or predict subsequent development of significant LV hypertrophy; and ii) whether preclinical signs of HCM are associated with increased risk of heart failure, atrial fibrillation, stroke, and SCD.

The presence of myocardial fibrosis can be observed frequently in HCM hearts, and its presence is believed to be a pathological substrate for cardiac arrhythmias and SCD. In the seminal study by Choudhury et al. (Mandorla et al.), myocardial scarring visualized by LGE was a common finding in asymptomatic or mildly symptomatic HCM patients. McCrohon et al. described a very high prevalence (about 80%) of LGE, which was associated with progressive ventricular dilation and incident clinical markers of SCD (McCrohon, Moon, and Prasad 2003). Adabag et al. documented a significant linear relationship between LGE and burden of ventricular arrhythmias on ambulatory ECG monitoring (Adabag et al. 2008). Finally, in a meta-analysis of 2,993 patients extent of LGE was strongly associated with the risk of SCD (pooled adjusted HR: 1.36/10% LGE; 95% CI: 1.10 to 1.69), even after adjustment for baseline characteristics. Awaiting data from randomized trials, quantitative LGE (Figure 7) is being more and more considered as a novel risk factor for SCD (Weng et al. 2016) and could be used as a potential arbitrator to arrive at a decision regarding ICD therapy for primary prevention of SCD in HCM patients in whom risk still remains ambiguous after assessment with current conventional risk factors (Maron 2012) (Figure 8).

Hyperintensity on T2-weighted short-tau inversion recovery CMR images - a sign of myocardial edema likely caused by ischemia due to microvascular impairment in HCM - was associated with advanced disease (higher LV mass index, lower LVEF and greater LGE extent), higher arrhythmic burden, signs of electrical instability and autonomic impairment (Todiere et al. 2014).

T1 mapping is an established technique for the assessment of diffuse myocardial interstitial fibrosis in HCM (Sado et al. 2013). However, the prognostic value of T1-mapping, especially concerning its potential role for arrhythmic risk stratification, remains undefined in HCM. In addition, little is known about prevalence and significance of myocardial fibrosis in genotype-positive/phenotype-negative HCM patients. Notably, among patients without overt LV hypertrophy, but with known genetic mutation, higher myocardial ECV was documented (Funabashi et al. 2013).

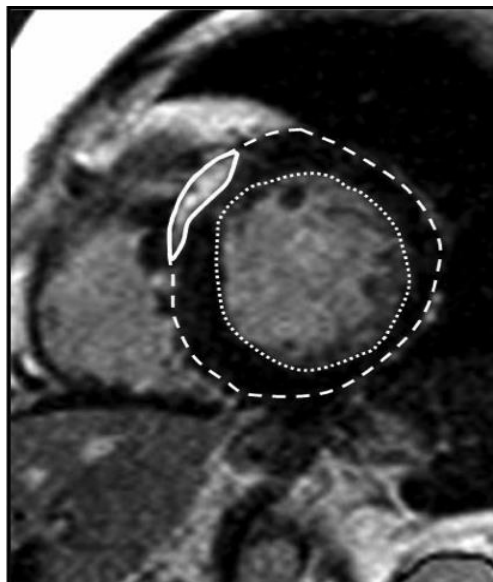


Figure 7. Late gadolinium enhancement (LGE) in a short axis view of a patient with hypertrophic cardiomyopathy: Endocardial (.....) and epicardial (-----) contours. % of LV mass with LGE assessed by visual planimetry (thick line). Reproduced with permission from Fluechter et al.: Extent of late gadolinium enhancement detected by cardiovascular magnetic resonance correlates with the inducibility of ventricular tachyarrhythmia in hypertrophic cardiomyopathy *Journal of Cardiovascular Magnetic Resonance* 2010;12:30.

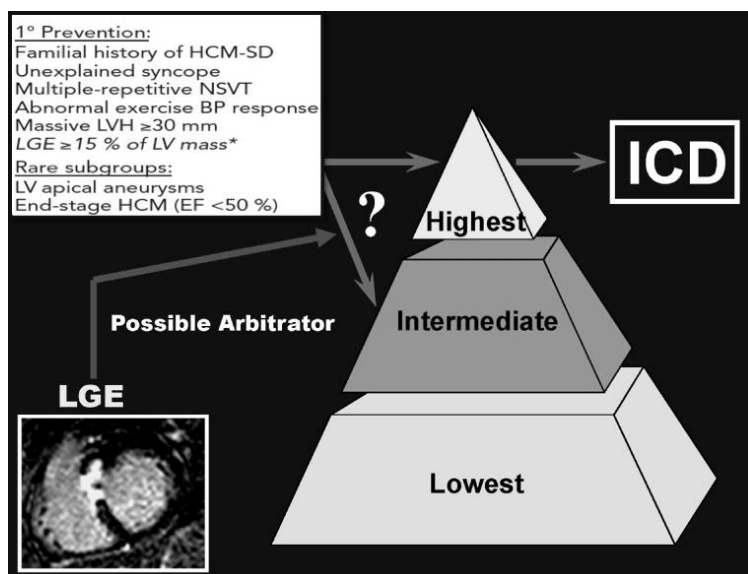


Figure 8. Role of CMR in sudden death risk stratification. Results of contrast-enhanced CMR with late gadolinium enhancement could be used as a potential arbitrator to arrive at a decision regarding ICD therapy for primary prevention of sudden death in HCM patients in whom risk still remains ambiguous after assessment with current conventional risk factors. Reproduced with permission from Maron et al.: Clinical Utility of Cardiovascular Magnetic Resonance in Hypertrophic Cardiomyopathy. *Journal of Cardiovascular Magnetic Resonance* 2012;14:13.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

ARVC/D is a genetic cardiomyopathy, with male predominance and an estimated prevalence varying from 1:2500 to 1:5000, characterized by progressive dystrophy and replacement of RV myocardium with adipose and fibrous tissue. Historically confined to the 'triangle of dysplasia' (including the RV outflow tract, the inferior diaphragmatic wall beneath the posterior leaflet of the tricuspid valve, and the apex of the RV) (van der Wall et al. 2000), ARVC/D is associated with increased risk of malignant ventricular arrhythmias, RV dysfunction and HF. Due to the frequent involvement of LV (>50% of cases), the term arrhythmogenic cardiomyopathy has been recently proposed (Haugaa et al. 2017). Autosomal recessive forms of ARVC/D - i.e., Naxos and Carvajal syndromes, caused respectively by mutations in genes encoding plakoglobin and desmoplakin - have been described, but most cases are caused by autosomal dominantly inherited mutations of genes encoding proteins of the desmosome complex of cardiomyocytes. Moreover, mutations in TGF- β , ryanodine receptor and titin genes have been associated with ARVC/D phenotype (Nijveldt et al. 2007).

Since the first description of ARVC/D more than 30 years ago (Botto et al.), considerable progresses have been made in the understanding of its pathogenesis, genetics, and diagnosis. Nevertheless, large prospective randomized trials on risk predictors and prognostic stratification still lack. Hence, therapeutic recommendations for this disease have been developed from observational studies and case series or adopted from other cardiomyopathies (Corrado et al. 2015).

The choice of treatment in ARVC/D is often an individualized decision based on patient presentation, risk assessment and physician judgment (Mandorla et al.).

In a cohort of 600 ICD recipients with ARVC/D, Schinkel et al. reported an annualized cardiac mortality rate of 0.9%, as well as an appropriate ICD intervention rate of approximately 10% (Schinkel 2013). The mean annual rate of inappropriate ICD interventions was approximately 4%. Such data strongly claim the need to improve current SCD risk stratification schemes.

The most challenging clinical dilemma in patients with ARVC/D concerns primary prevention of SCD. In this regard, current guidelines are scant, with unclear indications for prophylactic ICD therapy. Accordingly, in the absence of definite evidence-based parameters, accurate risk predictors of SCD in ARVC/D patients have to be clearly pinpointed. Several risk factors have been considered, including male gender, young age at presentation, one or more affected family member with SCD, unexplained syncope, ECG abnormalities, detection of non-sustained VT by ambulatory ECG monitoring, severe RV dilation and/or LV involvement by transthoracic echocardiography, and induction of VT during electrophysiological testing. Further, little is known as to whether the disease course is influenced by genotype. RV dilation, global RV dysfunction or regional wall motion abnormalities as assessed by different imaging techniques are the

cornerstone of ARVC/D diagnosis, but also independent predictors of SCD (Marcus et al. 2010, Hulot et al. 2004).

CMR is erroneously considered the ‘gold standard’ test to diagnose ARVC/D. As emphasized in the TFC 2010, the diagnosis of this disease is a composite of familiar, ECG, arrhythmic, histological, functional, and structural features, in which CMR may play a role only to the latter two aspects. The CMR parameters from the TFC 2010 include RV regional dysfunction, reduced RVEF and enlarged indexed RV end-diastole volume, as well as localized RV wall thinning and aneurysmal formations (Figure 9).

Broadly, CMR abnormalities can be divided into morphological (intramyocardial fat deposits, focal wall thinning, wall hypertrophy, trabecular disarray, and RV outflow tract enlargement) and functional (regional contraction abnormalities, aneurysms, RV global dilation/dysfunction, and RV diastolic dysfunction) changes (Botto et al.). Historically, the presence of fatty infiltration of the RV free wall at T1-weighted CMR images was the first-described CMR abnormality in ARVC/D (Wolf, Rose-Pittet, and Page 1989). It was found corresponding to areas of wall motion abnormalities, also inducible for VT. In addition, a correlation was found between lesion location and distribution seen at CMR and ex vivo histology in explanted hearts (Mandorla et al.). The presence of hyperintense areas in T1-weighted images can be found also in the LV and in the interventricular septum. However, due to coil proximity, breathing motion artifacts and limited CMR spatial resolution, detection of fat replacement by CMR is a challenging task.

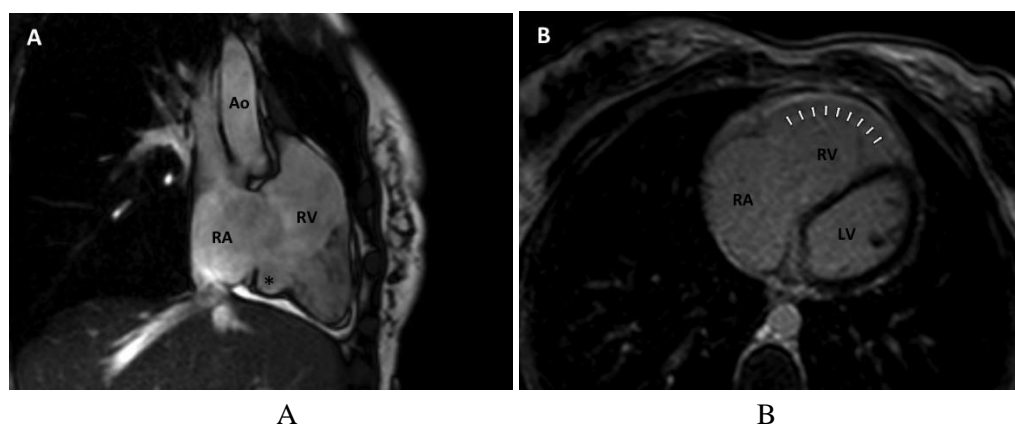


Figure 9. Findings suggestive of ARVC/D include A) localized aneurysms in the RV inflow tract (asterisk) and B) LGE of the RV free wall (arrows). Ao = aorta; RA = right atrium; RV = right ventricle.

Myocardial fat can be observed at CT and CMR imaging of healthy adults and in subjects with myocardial diseases other than ARVC/D (Kellman, Hernando, and Arai 2010), such as DCM (Lu et al. 2013), healed MI, cardiac lipoma, lipomatous hypertrophy of the interatrial septum, tuberous sclerosis complex, dilated cardiomyopathy and cardiomyopathy with muscular dystrophy. For all these reasons, CMR assessment of fatty

infiltration was not included in the original and revised diagnostic TFC for ARVC/D (Marcus et al. 2010). However, the presence of fat does represent a substrate for arrhythmias (due to the lower electrical conductivity of fat) and has been associated with SCD. Hence, noninvasive detection of intramyocardial fat has relevant prognostic value.

LGE of the RV wall was reported in various studies and correlates with fibro-fatty changes, inducible VT and severe RV dysfunction (Iles et al. 2008). LGE was also observed in the LV, particularly in familial forms of desmoplakin mutations, which exhibit a phenotype of left-dominant ARVC/D (Haugaa et al. 2017). Cine sequences may be used to assess RV volumes, with good interobserver correlation and optimal accuracy for ARVC/D diagnosis. RV morphological abnormalities are frequently found in the mid-cavity and basal regions. CMR assessment of LV involvement is essential to the delineation of three distinct patterns of disease expression: i) classic, with isolated RV disease or LV involvement in association with significant RV impairment; ii) left dominant, with early and prominent LV manifestations and relatively mild right-sided disease; iii) biventricular, characterized by parallel involvement of both ventricles. Of note, the TFC 2010 lacks specific diagnostic criteria for the nonclassical variants of ARVC/D. LV-LGE is a common finding in the setting of global RV dysfunction, located more frequently at the level of the infero-lateral wall and the infero-septal junction with typical subepicardial or midwall distribution, in agreement with histopathology (Sen-Chowdhry, Syrris, and Ward 2007); however, LV dominant phenotype can sometimes be unrecognized and misdiagnosed as myocarditis, DCM or HCM.

Sarcoidosis

Sarcoidosis is a systemic disorder characterized by noncaseating granulomatous infiltration that most commonly affects the lungs and lymph nodes. CS may appear at any point during the course of sarcoidosis, even in the absence of systemic or pulmonary symptoms, with three histological stages: edema, granulomatous infiltration and fibrosis leading to postinflammatory scarring. The hallmark of sarcoidosis is noncaseating epitheloid cell granulomas, surrounded by numerous lymphocytes and encased by a ring of fibroblasts, collagen and proteoglycans. Granulomas can involve any portion of the heart, including the conduction system and coronary arteries. In the majority of cases, the myocardium is firstly involved and the subsequent endocardial and pericardial involvement appear to be a direct extension of myocardial disease. The areas of involvement, in descending order of frequency, are LV free wall, interventricular septum, papillary muscles, RV and atria (Lynch et al. 2014). The extensive infiltration of the myocardium by noncaseating granulomas leads to HF, with either systolic or diastolic dysfunction, and development of ventricular aneurysms in 10% of patients. Papillary muscle dysfunction is associated with valvular incompetence in about 68% of patients,

while asymptomatic pericardial involvement has been reported in <10% of cases with extensive myocardial infiltration.

The most frequent finding in manifest CS is complete heart block, due to the involvement of basal septum by scar tissue or granulomas or to the ischemia of the nodal artery. Complete heart block occurs at a younger age in patients with CS, compared with patients with complete heart block of other causes. Thus, sarcoidosis should be included in the diagnostic work-up of young patients with syncope. Likewise, patients already diagnosed with sarcoidosis who present with syncope or pre-syncope should be always evaluated for complete heart block (Houston and Mukherjee 2014). However, CS is particularly difficult to diagnose because clinical manifestations are nonspecific, spanning from no symptoms to heart failure, and from conduction system disorders to ventricular arrhythmias. SCD may occur because of complete heart block or ventricular arrhythmias. In fact, sarcoid granulomas have the potential to create a pro-arrhythmogenic substrate paving the way to abnormal automaticity or reentrant VT. Atrial arrhythmias are less common than ventricular arrhythmias and occur in 15-17% of patients, resulting from atrial dilatation or pulmonary involvement. Evidence-based data supporting SCD risk stratification in patients with CS are limited. Remarkably, LGE imaging by CMR was first introduced as a potential arbitrator for primary prevention ICD decision making in the last consensus document on the diagnosis and management of arrhythmias associated with CS (Birnie et al. 2014).

Key points of CMR in CS include evaluation of extra-cardiac findings, ventricular dimensions, mass and function, biventricular regional wall motion abnormalities, edema and LGE imaging (Figure 10). LGE is a major diagnostic finding in CS patients, with the most common patterns of distribution including both mid-wall and subepicardial regions of the infero-lateral wall and the basal septum.

Granulomatous infiltrations of the RV have been described at autopsy in 42% of patients with arrhythmias or conduction block, HF and recurrent pericardial effusion (Hulten et al. 2016). Focal edema areas, as evaluated in T2-weighted sequences, are suggestive of active inflammation. LGE has been reported as a highly sensitive marker for cardiac involvement and an independent risk factor for ventricular arrhythmia, appropriate ICD therapy and death (Greulich et al. 2013). RV-LGE has been associated with an increased risk of adverse events in patients with CS and preserved ejection fraction, even in the absence of a prior history of VT, whereas patients with LGE and history of ventricular arrhythmias showed a high rate of recurrent VT. On the other hand, absence of LGE is associated with a very low risk of incident VT (Crawford et al. 2014).

T1- and T2-mapping are promising CMR applications useful to provide a quantitative assessment of individual therapeutic response (Crouser et al. 2014). However, mapping modules are currently only available for research purposes.

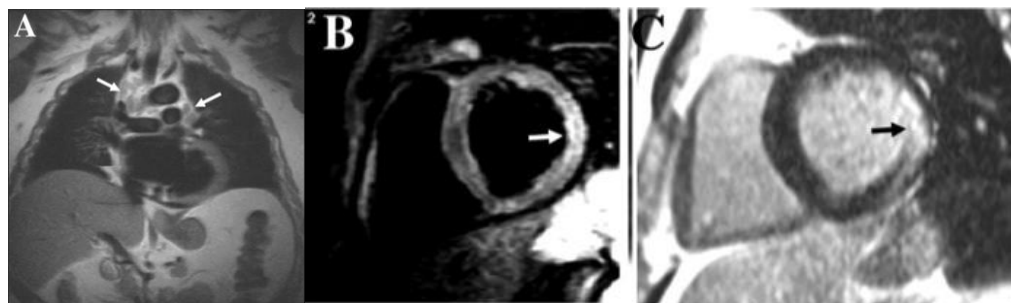


Figure 10. Cardiac sarcoidosis. Hilar lymphadenopathy on HASTE (A, arrows), localized edema in the lateral wall on STIR images (B, arrow) and mid-wall LGE (C, arrow) are suggestive of sarcoidosis. Reproduced with permission from Parsai et al.: Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. *Journal of Cardiovascular Magnetic Resonance* 2012;14:54.

Iron Overload Cardiomyopathy

IOC is defined as a secondary form of cardiomyopathy resulting from pathological iron accumulation in the myocardium, related to genetically determined disorder of iron metabolism or to multiple blood transfusions. Iron plays a pivotal role in erythropoiesis, oxygen delivery and storage and in many metabolic and enzymatic processes. Disorders of iron homeostasis leading to excessive iron intake and intracellular storage are harmful and associated to multiple organ damage. Target organs include the heart, the liver and the endocrine glands, the most frequent manifestations being LV dysfunction leading to HF, liver dysfunction progressing in cirrhosis, and endocrine abnormalities associated with hypothyroidism, diabetes mellitus and hypogonadism. IOC represents a major cause of morbidity and mortality in patients with thalassemia major and secondary iron overload conditions.

Iron overload, also known as hemochromatosis, results in lipid peroxidation and damage to mitochondrial respiratory enzyme chain of cardiomyocytes, interfering with electrical function and promotion of cardiac fibrosis. LV diastolic dysfunction is the first manifestation of IOC. Then, two phenotypes of IOC have been described: the restrictive phenotype, with restrictive filling and preserved LVEF, and the dilated one, characterized by progressive chamber dilatation and reduced LVEF. Restrictive cardiomyopathy constantly proceeds to dilated cardiomyopathy, if the cause of iron overload recurs and no proper iron chelation therapy is initiated. However, it is believed that the dilated phenotype is also related to the interactions between the primary disease and many immunologic and inflammatory factors or comorbidities, such as myocarditis; thus, it seems to have a multifactorial pathophysiology (Kremastinos and Farmakis 2011).

The natural course of the disease is characterized by preclinical myocardial iron accumulation, with subsequent onset of malignant bradi- or tachyarrhythmias, and eventually SCD or HF (Klitsch and Stiller 2004). In patients with thalassemia major, iron chelation therapy increased life expectancy, even though 5-year survival for patients presenting with HF was around 50% (Kremastinos et al. 2001). CMR is the best tool to quantify biventricular volumes and function parameters. Myocardial fibrosis as assessed by LGE imaging, shows a positive linear correlation with prevalent CV risk factors, incident cardiac complications and serum anti-hepatitis C virus antibodies.

Further, T2* CMR imaging is a unique technique for the quantification of myocardial iron overload and for tailoring iron chelation therapy. In particular, multislice multiecho T2* imaging has been validated as an effective and reproducible technique for the assessment of segmental and global myocardial iron distribution. Of note, T2* CMR significantly reduced acute decompensated HF episodes and cardiac mortality in chronically transfused TM patients by enabling individually tailored chelation regimens (Meloni et al. 2016).

In normal conditions, a high magnetic field is able to excite protons in the body, inducing homogenous microwave signals with a normal T2 tissue relaxation time. On the other hand, patients with cardiac iron overload show changes in signal intensity and susceptibility with shortening of the relaxation time and quicker darkening of the image due to paramagnetic effect of iron. The higher the concentration of iron store in the myocardium, the shorter the T2 and T2* relaxation times. T2* is equivalent to the summation of T2 tissue relaxation and local magnetic field inhomogeneity, also known as T2', that increase with iron deposition according to the equation: $1/T2^* = 1/T2 + 1/T2'$. The clinical severity of the iron overload is graded according to T2* values. Lower T2* values are significantly associated with the clinical severity of IOC and to the need for iron chelation therapy (Anderson et al. 2001, Tanner et al. 2006, Alpendurada et al. 2010). Patients with T2* >20 ms are at low risk for development of HF, while T2* between 10 and 20 ms and T2* less than 10 ms identify patients at intermediate and high risk of HF, respectively (Figure 11). In a cohort of patients affected by thalassemia major, HF occurred in 47% of patients with T2* < 6 ms, in 21% of patients with T2* between 6 and 10 ms and in 0.2% of patients with T2* >10 ms. After 1-year of follow-up, arrhythmias could be detected in 19%, 18% and 4% of IOC patients with T2* < 6 ms, T2* of 6-10 ms and T2* >10 ms, respectively (Kirk et al. 2009). Finally, normal cardiac T2* value yielded excellent negative predictive value for HF prediction (Patton et al. 2010). Further evidence about clinical and prognostic significance of native T1 mapping and ECV in patients with hemochromatosis is eagerly awaited (Alam et al. 2015).

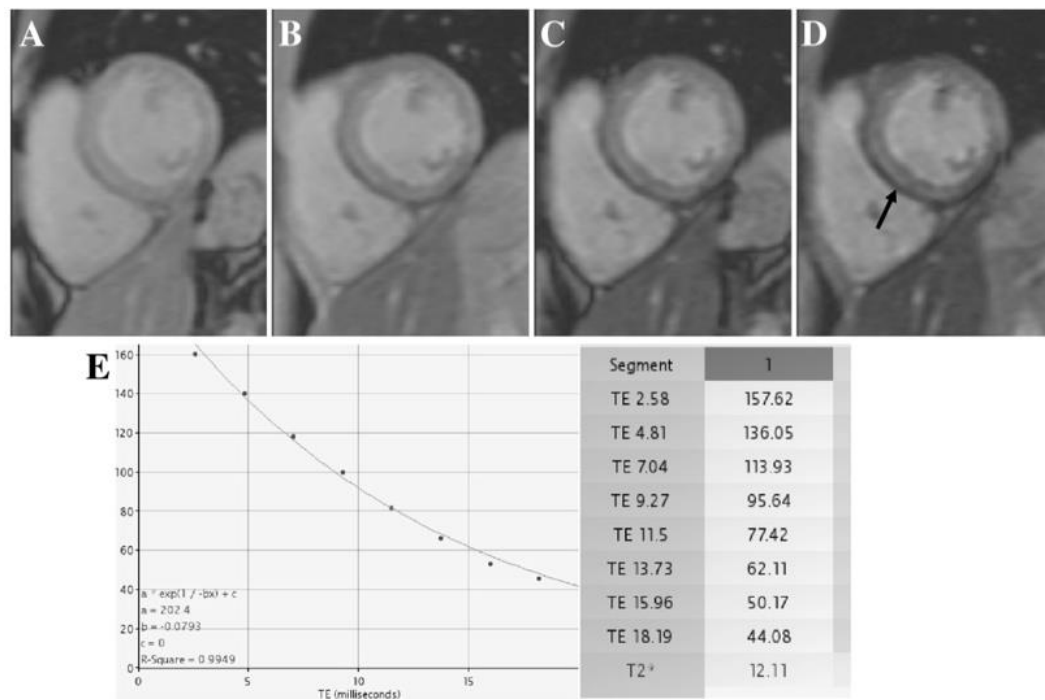


Figure 11. Iron overload cardiomyopathy. A mid-level gradient echo short-axis slice is imaged at different echo times (A: 2 ms to D: 14 ms) and T2*value is estimated from the signal intensity decay curve (E). Typical sub-epicardial iron deposition can be seen (arrow). Reproduced with permission, from Parsai et al.: Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. Journal of Cardiovascular Magnetic Resonance 2012;14:54.

Cardiac Amyloidosis

The term amyloidosis include a group of both inherited and acquired diseases characterized by a protein-based infiltrates in tissues as beta-pleated sheets. The subtype of the disease depends on which protein is infiltrating and the spectrum of systemic involvement can involve many organs such as kidneys, nervous system, liver and gastrointestinal system, lungs, skin, joints, bone, blood vessels and the heart. Amyloid may be related to more than 30 types of proteins, but only two do generally involve the heart: AL chain and ATTR. Light chains are proteins produced by an abnormally proliferative monoclonal population of plasma cells. On the other hand, transthyretin is a transporter of thyroxine and retinol produced by the liver and circulates mostly as a homo-tetramer, whereas a small amount circulates in monomeric form and is able to misfold and deposit as amyloid. Two main subtypes of ATTR amyoidosis have been identified: wild-type ATTR and mutant, hereditary ATTR. Patients with wild-type ATTR have a normal protein leading to a progressive tissue deposit, whereas mutant ATTR determines an accelerated amyloid deposition. In the heart, deposition of amyloid in the extracellular space may occur in the myocardium, pericardium, small vessels and

conduction system, leading to a restrictive cardiomyopathy with early diastolic dysfunction and subsequent biventricular systolic dysfunction and arrhythmias. Cardiac involvement is common in patients with AL or ATTR, and is by far the major cause of morbidity and mortality. Symptomatic cardiac involvement is usually associated with dyspnea, peripheral edema, cachexia and ascites, whereas syncope is more frequently related to CV dysautonomia than to ventricular arrhythmias. Patients with advanced cardiac dysfunction may experience SCD, likely a multifactorial process. Ventricular arrhythmias are related to severe myocardial infiltration leading also to increased electromechanical dissociation. Moreover, severe conduction disease may also determine complete atrio-ventricular block and cardiac arrest (Banypersad et al. 2012).

The commonest form of amyloidosis is that associated with a plasma cell dyscrasia, with an incidence of 6-10 cases per million population per year. Patients with AL amyloidosis have a median survival <5 years and the presence of symptomatic cardiac involvement at diagnosis configures a negative prognostic marker. On the other hand, the prognosis of ATTR is generally 3 to 5 years. However, in both forms, myocardial involvement is the main determinant of prognosis and, thus, better diagnostic tests could make quicker identification and treatment for CA. CMR represents a good alternative to echocardiography to evaluate morphology and function and to depict a broader range of differences between the two main amyloidosis subtypes. LGE imaging has an excellent diagnostic accuracy for the diagnosis of cardiac amyloid. The typical LGE pattern with diffuse subendocardial involvement and noncoronary distribution, and the abnormal gadolinium kinetics of myocardium and blood pool (early darkening of blood pool, nulling defect of myocardium) are pathognomonic of cardiac amyloidosis (Figure 12) (Pontone et al. 2017, Syed et al. 2010).

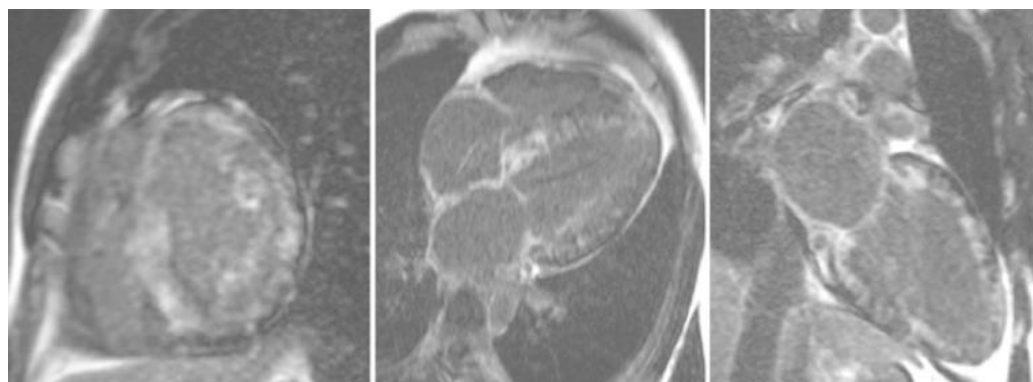


Figure 12. Amyloidosis with a typical circumferential diffuse enhancement (‘zebra’ pattern). Reproduced with permission from Parsai et al.: Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies. *Journal of Cardiovascular Magnetic Resonance* 2012;14:54.

The severity of cardiac amyloidosis can be estimated by ventricular wall thickness, left ventricular mass and LGE extension. Cardiac amyloid deposition is commonly more extensive in ATTR type than in the AL. On the other hand, AL type is associated with greater release of cardiac biomarkers, higher degree of diastolic dysfunction and an overall worse prognosis (Dungu et al. 2014). It has been assumed that AL amyloid may have a direct toxic effect on myocardium or a more rapid deposition than ATTR, leading to a different extent of myocardial damage and prognosis. Nevertheless, LGE is associated with all-cause mortality in patients with both AL and ATTR cardiac amyloidosis (Fontana et al. 2015).

Another prognostic parameter in patients with systemic AL is left atrial ejection fraction, strongly associated with NYHA functional class, the Mayo Clinic stage of the disease, LGE and 2-year all-cause mortality (Mohty et al. 2016).

The diagnostic accuracy of new CMR parametric techniques has been recently evaluated and both native T1 and ECV are promising techniques for the early detection of cardiac amyloidosis. In particular, native T1 showed a good correlation with parameters of systolic and diastolic dysfunction, and was found to be more sensitive than LGE in the early stage of the disease (Karamitsos et al. 2013). However, larger studies are needed to confirm such preliminary results.

REFERENCES

- The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. 1997. "A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias." *N Engl J Med* no. 337 (22):1576-83. doi: 10.1056/NEJM199711273372202.
- Adabag, A. S., B. J. Maron, E. Appelbaum, C. J. Harrigan, J. L. Buros, C. M. Gibson, J. R. Lesser, C. A. Hanna, J. E. Udelson, W. J. Manning, and M. S. Maron. 2008. "Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance." *J Am Coll Cardiol* no. 51 (14):1369-74. doi: 10.1016/j.jacc.2007.11.071.
- Alam, MH., D. Auger, GC. Smith, T. He, V. Vassiliou, A. Baksi, R. Wage, P. Drivas, Y. Feng, DN. Firmin, and DJ. Pennell. 2015. "T1 at 1.5T and 3T compared with conventional T2* at 1.5T for cardiac siderosis." *J Cardiovasc Magn Reson.* no. 17 (102):1-11. doi: 10.1186/s12968-015-0207-0.
- Aleksova, A., G. Sabbadini, M. Merlo, B. Pinamonti, G. Barbati, M. Zecchin, R. Bussani, F. Silvestri, A. M. Iorio, D. Stolfo, M. Dal Ferro, A. M. Dragos, G. Meringolo, S. Pyxaras, F. Lo Giudice, A. Perkan, A. di Lenarda, and G. Sinagra. 2009. "Natural history of dilated cardiomyopathy: from asymptomatic left ventricular dysfunction to heart failure--a subgroup analysis from the Trieste Cardiomyopathy Registry." *J*

- Cardiovasc Med (Hagerstown)* no. 10 (9):699-705. doi: 10.2459/JCM.0b013e32832bba35.
- Aljaroudi, W. A., S. D. Flamm, W. Saliba, B. L. Wilkoff, and D. Kwon. 2013. "Role of CMR imaging in risk stratification for sudden cardiac death." *JACC Cardiovasc Imaging* no. 6 (3):392-406. doi: 10.1016/j.jcmg.2012.11.011.
- Alpendurada, F., JP. Carpenter, M. Deac, P. Kirk, JM. Walker, JB. Porter, W. Banya, T. He, GC. Smith, and DJ. Pennell. 2010. "Relation of myocardial T2* to right ventricular function in thalassaemia major." *Eur Heart J* no. 31 (13):1648-1654.
- Anderson, LJ., S. Holden, B. Davis, E. Prescott, CC. Charrier, NH. Bunce, DN. Firmin, B. Wonke, J. Porter, JM. Walker, and Pennell DJ. 2001. "Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload." *Eur Heart J* no. 22 (23):2171-2179.
- Assomull, R.G., S.K. Prasad, and J. Lyne. 2006. "Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy." *J Am Coll Cardiol* no. 48:1977-1985.
- Authors/Task Force, members, P. M. Elliott, A. Anastasakis, M. A. Borger, M. Borggrefe, F. Cecchi, P. Charron, A. A. Hagege, A. Lafont, G. Limongelli, H. Mahrholdt, W. J. McKenna, J. Mogensen, P. Nihoyannopoulos, S. Nistri, P. G. Pieper, B. Pieske, C. Rapezzi, F. H. Rutten, C. Tillmanns, and H. Watkins. 2014. "2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC)." *Eur Heart J* no. 35 (39):2733-79. doi: 10.1093/eurheartj/ehu284.
- Banypersad, SM., JC. Moon, C. Whelan, PN. Hawkins, and AD. Wechalekar. 2012. "Updates in Cardiac Amyloidosis: A Review." *J Am Heart Assoc.* no. 1 (2):e000364.
- Bardy, G. H., K. L. Lee, D. B. Mark, J. E. Poole, D. L. Packer, R. Boineau, M. Domanski, C. Troutman, J. Anderson, G. Johnson, S. E. McNulty, N. Clapp-Channing, L. D. Davidson-Ray, E. S. Fraulo, D. P. Fishbein, R. M. Luceri, J. H. Ip, and Investigators Sudden Cardiac Death in Heart Failure Trial. 2005. "Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure." *N Engl J Med* no. 352 (3):225-37. doi: 10.1056/NEJMoa043399.
- Bello, D., D. S. Fieno, R. J. Kim, F. S. Pereles, R. Passman, G. Song, A. H. Kadish, and J. J. Goldberger. 2005. "Infarct morphology identifies patients with substrate for sustained ventricular tachycardia." *J Am Coll Cardiol* no. 45 (7):1104-8. doi: 10.1016/j.jacc.2004.12.057.
- Betgem, R. P., G. A. de Waard, R. Nijveldt, A. M. Beek, J. Escaned, and N. van Royen. 2015. "Intramyocardial haemorrhage after acute myocardial infarction." *Nat Rev Cardiol* no. 12 (3):156-67. doi: 10.1038/nrcardio.2014.188.
- Bigger, J. T., Jr. 1997. "Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery.

- Coronary Artery Bypass Graft (CABG) Patch Trial Investigators." *N Engl J Med* no. 337 (22):1569-75. doi: 10.1056/NEJM199711273372201.
- Birnie, DH., WH. Sauer, F. Bogun, JM. Cooper, DA. Culver, CS. Duvernoy, MA. Judson, J. Kron, D. Mehta, NJ. Cossedis, AR. Patel, T. Ohe, P. Raatikainen, and K. Soejima. 2014. "HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis." *Heart Rhythm* no. 11:1305-1323.
- Bolick, D. R., D. B. Hackel, K. A. Reimer, and R. E. Ideker. 1986. "Quantitative analysis of myocardial infarct structure in patients with ventricular tachycardia." *Circulation* no. 74 (6):1266-79.
- Botto, F., P. Alonso-Coello, M. T. Chan, J. C. Villar, D. Xavier, S. Srinathan, G. Guyatt, P. Cruz, M. Graham, C. Y. Wang, O. Berwanger, R. M. Pearse, B. M. Biccadd, V. Abraham, G. Malaga, G. S. Hillis, R. N. Rodseth, D. Cook, C. A. Polanczyk, W. Szczeklik, D. I. Sessler, T. Sheth, G. L. Ackland, M. Leuwer, A. X. Garg, Y. Lemanach, S. Pettit, D. Heels-Ansdell, G. Luratibuse, M. Walsh, R. Sapsford, H. J. Schunemann, A. Kurz, S. Thomas, M. Mrkobrada, L. Thabane, H. Gerstein, P. Paniagua, P. Nagele, P. Raina, S. Yusuf, P. J. Devereaux, P. J. Devereaux, D. I. Sessler, M. Walsh, G. Guyatt, M. J. McQueen, M. Bhandari, D. Cook, J. Bosch, N. Buckley, S. Yusuf, C. K. Chow, G. S. Hillis, R. Halliwell, S. Li, V. W. Lee, J. Mooney, C. A. Polanczyk, M. V. Furtado, O. Berwanger, E. Suzumura, E. Santucci, K. Leite, J. A. Santo, C. A. Jardim, A. B. Cavalcanti, H. P. Guimaraes, M. J. Jacka, M. Graham, F. McAlister, S. McMurtry, D. Townsend, N. Pannu, S. Bagshaw, A. Bessissow, M. Bhandari, E. Ducepe, J. Eikelboom, J. Ganame, J. Hankinson, S. Hill, S. Jolly, A. Lamy, E. Ling, P. Magloire, G. Pare, D. Reddy, D. Szalay, J. Tittley, J. Weitz, R. Whitlock, S. Darvish-Kazim, J. Debeer, P. Kavsak, C. Kearon, R. Mizera, M. O'Donnell, M. McQueen, J. Pinthus, S. Ribas, M. Simunovic, V. Tandon, T. Vanhelder, M. Winemaker, H. Gerstein, S. McDonald, P. O'Bryne, A. Patel, J. Paul, Z. Punthakee, K. Raymer, O. Salehian, F. Spencer, S. Walter, A. Worster, A. Adili, C. Clase, D. Cook, M. Crowther, J. Douketis, A. Gangji, P. Jackson, W. Lim, P. Lovrics, S. Mazzadi, W. Orovan, J. Rudkowski, M. Soth, M. Tiboni, R. Acedillo, A. Garg, A. Hildebrand, N. Lam, D. Macneil, M. Mrkobrada, P. S. Roshanov, S. K. Srinathan, C. Ramsey, P. S. John, L. Thorlacius, F. S. Siddiqui, H. P. Grocott, A. McKay, T. W. Lee, R. Amadeo, D. Funk, H. McDonald, J. Zacharias, J. C. Villar, O. L. Cortes, M. S. Chaparro, S. Vasquez, A. Castaneda, S. Ferreira, P. Coriat, D. Monneret, J. P. Goarin, C. I. Esteve, C. Royer, G. Daas, M. T. Chan, G. Y. Choi, T. Gin, L. C. Lit, D. Xavier, A. Sigamani, A. Faruqui, R. Dhanpal, S. Almeida, J. Cherian, S. Furrugh, V. Abraham, L. Afzal, P. George, S. Mala, H. Schunemann, P. Muti, E. Vizza, C. Y. Wang, G. S. Ong, M. Mansor, A. S. Tan, Shariffuddin, II, V. Vasanthan, N. H. Hashim, A. W. Undok, U. Ki, H. Y. Lai, W. A. Ahmad, A. H. Razack, G. Malaga, V. Valderrama-Victoria, J. D. Loza-Herrera, M. De Los Angeles Lazo, A. Rotta-Rotta, W. Szczeklik, B. Sokolowska, J. Musial, J. Gorka, P.

- Iwaszczuk, M. Kozka, M. Chwala, M. Raczek, T. Mrowiecki, B. Kaczmarek, B. Biccard, H. Cassimjee, D. Gopalan, T. Kisten, A. Mugabi, P. Naidoo, R. Naidoo, R. Rodseth, D. Skinner, A. Torborg, P. Paniagua, G. Urrutia, M. L. Maestre, M. Santalo, R. Gonzalez, A. Font, C. Martinez, X. Pelaez, M. De Antonio, J. M. Villamor, J. A. Garcia, M. J. Ferre, E. Popova, P. Alonso-Coello, I. Garutti, P. Cruz, C. Fernandez, M. Palencia, S. Diaz, T. Del Castillo, A. Varela, A. de Miguel, M. Munoz, P. Pineiro, G. Cusati, M. Del Barrio, M. J. Membrillo, D. Orozco, F. Reyes, R. J. Sapsford, J. Barth, J. Scott, A. Hall, S. Howell, M. Lobley, J. Woods, S. Howard, J. Fletcher, N. Dewhirst, C. Williams, A. Rushton, I. Welters, M. Leuwer, R. Pearse, G. Ackland, A. Khan, E. Niebrzegowska, S. Benton, A. Wragg, A. Archbold, A. Smith, E. McAlees, C. Ramballi, N. Macdonald, M. Januszewska, R. Stephens, A. Reyes, L. G. Paredes, P. Sultan, D. Cain, J. Whittle, A. G. Del Arroyo, D. I. Sessler, A. Kurz, Z. Sun, P. S. Finnegan, C. Egan, H. Honar, A. Shahinyan, K. Panjasawatwong, A. Y. Fu, S. Wang, E. Reineks, P. Nagele, J. Blood, M. Kalin, D. Gibson, T. Wildes, on behalf of The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Investigators, Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Writing Group, N. Study Investigators Writing Group Appendix 1. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation, N. Operations Committee Appendix 2. The Vascular Events in Noncardiac Surgery Patients Cohort Evaluation, and N. Vision Study Investigators Vascular Events in Noncardiac Surgery Patients Cohort Evaluation. 2014. "Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes." *Anesthesiology* no. 120 (3):564-78. doi: 10.1097/ALN.000000000000113.
- Boye, P., H. Abdel-Aty, U. Zacharzowsky, S. Bohl, C. Schwenke, R. J. van der Geest, R. Dietz, A. Schirdewan, and J. Schulz-Menger. 2011. "Prediction of life-threatening arrhythmic events in patients with chronic myocardial infarction by contrast-enhanced CMR." *JACC Cardiovasc Imaging* no. 4 (8):871-9. doi: 10.1016/j.jcmg.2011.04.014.
- Burt, J. R., S. L. Zimmerman, I. R. Kamel, M. Halushka, and D. A. Bluemke. 2014. "Myocardial T1 mapping: techniques and potential applications." *Radiographics* no. 34 (2):377-95. doi: 10.1148/rg.342125121.
- Buxton, A. E., K. E. Ellison, P. Lorrvidhaya, and O. Ziv. 2010. "Left ventricular ejection fraction for sudden death risk stratification and guiding implantable cardioverter-defibrillators implantation." *J Cardiovasc Pharmacol* no. 55 (5):450-5.
- Buxton, A. E., K. L. Lee, J. D. Fisher, M. E. Josephson, E. N. Prystowsky, and G. Hafley. 1999. "A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators." *N Engl J Med* no. 341 (25):1882-90. doi: 10.1056/NEJM199912163412503.

- Buxton, A. E., K. L. Lee, G. E. Hafley, L. A. Pires, J. D. Fisher, M. R. Gold, M. E. Josephson, M. H. Lehmann, E. N. Prystowsky, and Mustt Investigators. 2007. "Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study." *J Am Coll Cardiol* no. 50 (12):1150-7. doi: 10.1016/j.jacc.2007.04.095.
- Catalano, O., G. Moro, M. Perotti, M. Frascaroli, M. Ceresa, S. Antonaci, P. Baiardi, C. Napolitano, M. Baldi, and S. G. Priori. 2012. "Late gadolinium enhancement by cardiovascular magnetic resonance is complementary to left ventricle ejection fraction in predicting prognosis of patients with stable coronary artery disease." *J Cardiovasc Magn Reson* no. 14:29. doi: 10.1186/1532-429X-14-29.
- Codd, M. B., D. D. Sugrue, B. J. Gersh, and L. J. Melton, 3rd. 1989. "Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984." *Circulation* no. 80 (3):564-72.
- Connolly, S. J., M. Gent, R. S. Roberts, P. Dorian, D. Roy, R. S. Sheldon, L. B. Mitchell, M. S. Green, G. J. Klein, and B. O'Brien. 2000. "Canadian implantable defibrillator study (CIDS) : a randomized trial of the implantable cardioverter defibrillator against amiodarone." *Circulation* no. 101 (11):1297-302.
- Connolly, S. J., A. P. Hallstrom, R. Cappato, E. B. Schron, K. H. Kuck, D. P. Zipes, H. L. Greene, S. Boczor, M. Domanski, D. Follmann, M. Gent, and R. S. Roberts. 2000. "Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study." *Eur Heart J* no. 21 (24):2071-8. doi: 10.1053/euhj.2000.2476.
- Corrado, D., T. Wichter, M. S. Link, R. N. Hauer, F. E. Marchlinski, A. Anastakis, B. Bauce, C. Basso, C. Bruckhorst, A. Tsatsopoulou, H. Tandri, M. Paul, C. Schmied, A. Pelliccia, F. Duru, N. Protonotarios, N. M. Estes, 3rd, W. J. McKenna, G. Thiene, F. I. Marcus, and H. Calkins. 2015. "Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An International Task Force Consensus Statement." *Circulation* no. 132 (5):441-53. doi: 10.1161/CIRCULATIONAHA.115.017944.
- Crawford, T., J. Cowger, B. Desjardins, H. M. Kim, E. Good, K. Jongnarangsin, H. Oral, A. Chugh, F. Pelosi, F. Morady, and F. Bogun. 2010. "Determinants of postinfarction ventricular tachycardia." *Circ Arrhythm Electrophysiol* no. 3 (6):624-31. doi: 10.1161/CIRCEP.110.945295.
- Crawford, T., G. Mueller, S. Sarsam, H. Prasitdumrong, N. Chaiyen, X. Gu, J. Schuller, J. Kron, K. A. Nour, A. Cheng, S. Y. Ji, S. Feinstein, S. Gupta, K. Ilg, M. Sinno, S. Abu-Hashish, M. Al-Mallah, W. H. Sauer, K. Ellenbogen, F. Morady, and F. Bogun. 2014. "Magnetic resonance imaging for identifying patients with cardiac sarcoidosis and preserved or mildly reduced left ventricular function at risk of ventricular arrhythmias." *Circ Arrhythm Electrophysiol*. no. 7 (6):1109-15.

- Crouser, ED., C. Ono, T. Tran, X. He, and SV. Raman. 2014. "Improved Detection of Cardiac Sarcoidosis Using Magnetic Resonance with Myocardial T2 Mapping.." *Am J Respir Crit Care Med.* no. 189:109-12.
- Dagres, N., and G. Hindricks. 2013. "Risk stratification after myocardial infarction: is left ventricular ejection fraction enough to prevent sudden cardiac death?" *Eur Heart J* no. 34 (26):1964-71. doi: 10.1093/eurheartj/eh109.
- Dall'Armellina, E., S. K. Piechnik, V. M. Ferreira, Q. L. Si, M. D. Robson, J. M. Francis, F. Cuculi, R. K. Kharbanda, A. P. Banning, R. P. Choudhury, T. D. Karamitsos, and S. Neubauer. 2012. "Cardiovascular magnetic resonance by non-contrast T1-mapping allows assessment of severity of injury in acute myocardial infarction." *J Cardiovasc Magn Reson* no. 14:15. doi: 10.1186/1532-429X-14-15.
- De Bakker, J. M., F. J. van Capelle, M. J. Janse, A. A. Wilde, R. Coronel, A. E. Becker, K. P. Dingemans, N. M. van Hemel, and R. N. Hauer. 1988. "Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation." *Circulation* no. 77 (3):589-606.
- De Haan, S., T. A. Meijers, P. Knaapen, A. M. Beek, A. C. van Rossum, and C. P. Allaart. 2011. "Scar size and characteristics assessed by CMR predict ventricular arrhythmias in ischaemic cardiomyopathy: comparison of previously validated models." *Heart* no. 97 (23):1951-6. doi: 10.1136/heartjnl-2011-300060.
- Di Marco, A., I. Anguera, M. Schmitt, I. Klem, T. Neilan, J. A. White, M. Sramko, P. G. Masci, A. Barison, P. McKenna, I. Mordi, K. H. Haugaa, F. Leyva, J. Rodriguez Capitan, H. Satoh, T. Nabeta, P. D. Dallaglio, N. G. Campbell, X. Sabate, and A. Cequier. 2016. "Late Gadolinium Enhancement and the Risk for Ventricular Arrhythmias or Sudden Death in Dilated Cardiomyopathy: Systematic Review and Meta-Analysis." *JACC Heart Fail.* doi: 10.1016/j.jchf.2016.09.017.
- Dickstein, K., J. Kjekshus, and Optimaal Steering Committee of the OPTIMAAL Study Group. 2002. "Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan." *Lancet* no. 360 (9335):752-60.
- Dorian, P., S. H. Hohnloser, K. E. Thorpe, R. S. Roberts, K. H. Kuck, M. Gent, and S. J. Connolly. 2010. "Mechanisms underlying the lack of effect of implantable cardioverter-defibrillator therapy on mortality in high-risk patients with recent myocardial infarction: insights from the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT)." *Circulation* no. 122 (25):2645-52. doi: 10.1161/CIRCULATIONAHA.109.924225.
- Dungu, JN., O. Valencia, JH. Pinney, SD. Gibbs, D. Rowczenio, JA. Gilbertson, HJ. Lachmann, A. Wechalekar, JD. Gillmore, CJ. Whelan, PN. Hawkins, and LJ. Anderson. 2014. "CMR-based differentiation of AL and ATTR cardiac amyloidosis." *JACC Cardiovasc Imaging.* no. 7 (2):133-42.

- Elliott, P., C. O'Mahony, P. Syrris, A. Evans, C. Rivera Sorensen, M. N. Sheppard, G. Carr-White, A. Pantazis, and W. J. McKenna. 2010. "Prevalence of desmosomal protein gene mutations in patients with dilated cardiomyopathy." *Circ Cardiovasc Genet* no. 3 (4):314-22. doi: 10.1161/CIRCGENETICS.110.937805.
- Epstein, A. E., J. P. DiMarco, K. A. Ellenbogen, N. A. Estes, 3rd, R. A. Freedman, L. S. Gettes, A. M. Gillinov, G. Gregoratos, S. C. Hammill, D. L. Hayes, M. A. Hlatky, L. K. Newby, R. L. Page, M. H. Schoenfeld, M. J. Silka, L. W. Stevenson, M. O. Sweeney, S. C. Smith, Jr., A. K. Jacobs, C. D. Adams, J. L. Anderson, C. E. Buller, M. A. Creager, S. M. Ettinger, D. P. Faxon, J. L. Halperin, L. F. Hiratzka, S. A. Hunt, H. M. Krumholz, F. G. Kushner, B. W. Lytle, R. A. Nishimura, J. P. Ornato, R. L. Page, B. Riegel, L. G. Tarkington, C. W. Yancy, Guidelines American College of Cardiology/American Heart Association Task Force on Practice, Surgery American Association for Thoracic, and Surgeons Society of Thoracic. 2008. "ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons." *J Am Coll Cardiol* no. 51 (21):e1-62. doi: 10.1016/j.jacc.2008.02.032.
- Ezekowitz, J. A., P. W. Armstrong, and F. A. McAlister. 2003. "Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials." *Ann Intern Med* no. 138 (6):445-52.
- Fishman, G. I., S. S. Chugh, J. P. Dimarco, C. M. Albert, M. E. Anderson, R. O. Bonow, A. E. Buxton, P. S. Chen, M. Estes, X. Jouven, R. Kwong, D. A. Lathrop, A. M. Mascette, J. M. Nerbonne, B. O'Rourke, R. L. Page, D. M. Roden, D. S. Rosenbaum, N. Sotoodehnia, N. A. Trayanova, and Z. J. Zheng. 2010. "Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop." *Circulation* no. 122 (22):2335-48. doi: 10.1161/CIRCULATIONAHA.110.976092.
- Flett, A. S., J. Hasleton, C. Cook, D. Hausenloy, G. Quarta, C. Ariti, V. Muthurangu, and J. C. Moon. 2011. "Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance." *JACC Cardiovasc Imaging* no. 4 (2):150-6. doi: 10.1016/j.jcmg.2010.11.015.
- Fontana, M., SM. Banypersad, TA. Treibel, A. Abdel-Gadir, V. Maestrini, T. Lane, JA. Gilbertson, DF. Hutt, HJ. Lachmann, CJ. Whelan, AD. Wechalekar, AS. Herrey, JD. Gillmore, PN. Hawkins, and JC. Moon. 2015. "Differential Myocyte Responses in Patients with Cardiac Transthyretin Amyloidosis and Light-Chain Amyloidosis: A Cardiac MR Imaging Study." *Radiology*. no. 277 (2):388-97.

- Franciosa, J.A., M. Wilen, and S. Ziesche. "Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy." *Am J Cardiol* (51):831–836.
- Funabashi, N., H. Takaoka, S. Horie, K. Ozawa, M. Daimon, M. Takahashi, R. Yajima, M. Saito, K. Fujiwara, A. Tani, T. Kamata, M. Uehara, A. Kataoka, and Y. Kobayashi. 2013. "Regional peak longitudinal-strain by 2D speckle-tracking TTE provides useful information to distinguish fibrotic from non-fibrotic lesions in LV myocardium on cardiac MR in hypertrophic cardiomyopathy." *Int J Cardiol* no. 168 (4):4520-3. doi: 10.1016/j.ijcard.2013.06.105.
- Gao, P., R. Yee, L. Gula, A. D. Krahn, A. Skanes, P. Leong-Sit, G. J. Klein, J. Stirrat, N. Fine, L. Pallaveshi, G. Wisenberg, T. R. Thompson, F. Prato, M. Drangova, and J. A. White. 2012. "Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging." *Circ Cardiovasc Imaging* no. 5 (4):448-56. doi: 10.1161/CIRCIMAGING.111.971549.
- Germans, T., I. K. Russel, M. J. Gotte, M. D. Spreeuwenberg, P. A. Doevendans, Y. M. Pinto, R. J. van der Geest, J. van der Velden, A. A. Wilde, and A. C. van Rossum. 2010. "How do hypertrophic cardiomyopathy mutations affect myocardial function in carriers with normal wall thickness? Assessment with cardiovascular magnetic resonance." *J Cardiovasc Magn Reson* no. 12:13. doi: 10.1186/1532-429X-12-13.
- Gersh, B.J., B.J. Maron, and R.O. Bonow. 2011. "2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." *Circulation* no. 124:783–831.
- Goldberger, J. J., M. E. Cain, S. H. Hohnloser, A. H. Kadish, B. P. Knight, M. S. Lauer, B. J. Maron, R. L. Page, R. S. Passman, D. Siscovick, W. G. Stevenson, D. P. Zipes, Association American Heart, Foundation American College of Cardiology, and Society Heart Rhythm. 2008. "American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society Scientific Statement on Noninvasive Risk Stratification Techniques for Identifying Patients at Risk for Sudden Cardiac Death. A scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention." *J Am Coll Cardiol* no. 52 (14):1179-99. doi: 10.1016/j.jacc.2008.05.003.
- Goldenberg, I., J. Gillespie, A. J. Moss, W. J. Hall, H. Klein, S. McNitt, M. W. Brown, I. Cygankiewicz, W. Zareba, and Trial Executive Committee of the Multicenter Automatic Defibrillator Implantation, II. 2010. "Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-

- up study of the Multicenter Automatic Defibrillator Implantation Trial II.” *Circulation* no. 122 (13):1265-71. doi: 10.1161/CIRCULATIONAHA.110.940148.
- Goldenberg, I., A. J. Moss, W. J. Hall, S. McNitt, W. Zareba, M. L. Andrews, D. S. Cannom, and I. I. Investigators Multicenter Automatic Defibrillator Implantation Trial. 2006. “Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II.” *Circulation* no. 113 (24):2810-7. doi: 10.1161/CIRCULATIONAHA.105.577262.
- Goldenberg, I., A. K. Vyas, W. J. Hall, A. J. Moss, H. Wang, H. He, W. Zareba, S. McNitt, M. L. Andrews, and MADIT-II Investigators. 2008. “Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction.” *J Am Coll Cardiol* no. 51 (3):288-96. doi: 10.1016/j.jacc.2007.08.058.
- Gorgels, A. P., C. Gijssbers, J. de Vreede-Swagemakers, A. Lousberg, and H. J. Wellens. 2003. “Out-of-hospital cardiac arrest--the relevance of heart failure. The Maastricht Circulatory Arrest Registry.” *Eur Heart J* no. 24 (13):1204-9.
- Greenberg, H., R. B. Case, A. J. Moss, M. W. Brown, E. R. Carroll, M. L. Andrews, and MADIT-II Investigators. 2004. “Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II).” *J Am Coll Cardiol* no. 43 (8):1459-65. doi: 10.1016/j.jacc.2003.11.038.
- Greulich, S., CC. Deluigi, S. Gloekler, A. Wahl, C. Zurn, U. Kramer, D. Nothnagel, H. Bultel, J. Schumm, S. Grun, P. Ong, A. Wagner, S. Schneider, K. Nassenstein, M. Gawaz, U. Sechtem, O. Bruder, and H. Mahrholdt. 2013. “CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis.” *JACC Cardiovasc Imaging* no. 6:501-511.
- Grimm, W., M. Christ, and J. Bach. 2003. “Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study.” *Circulation* no. 108:2883-2891.
- Gulati, A., A. Jabbour, T. F. Ismail, K. Guha, J. Khwaja, S. Raza, K. Morarji, T. D. Brown, N. A. Ismail, M. R. Dweck, E. Di Pietro, M. Roughton, R. Wage, Y. Daryani, R. O'Hanlon, M. N. Sheppard, F. Alpendurada, A. R. Lyon, S. A. Cook, M. R. Cowie, R. G. Assomull, D. J. Pennell, and S. K. Prasad. 2013. “Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy.” *JAMA* no. 309 (9):896-908. doi: 10.1001/jama.2013.1363.
- Haugaa, K. H., C. Basso, L. P. Badano, C. Bucciarelli-Ducci, N. Cardim, O. Gaemperli, M. Galderisi, G. Habib, J. Knuuti, P. Lancellotti, W. McKenna, D. Neglia, B. A. Popescu, and T. Edvardsen. 2017. “Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy-an expert consensus document of the European Association of Cardiovascular Imaging.” *Eur Heart J Cardiovasc Imaging*. doi: 10.1093/ehjci/jew229.

- Heydari, B., and R. Y. Kwong. 2014. "Cardiac magnetic resonance infarct heterogeneity: is it ready to be used on patients for the prevention of sudden cardiac death?" *Eur Heart J Cardiovasc Imaging* no. 15 (1):108-9. doi: 10.1093/ehjci/jet188.
- Hill, S. F., and M. N. Sheppard. 2010. "Non-atherosclerotic coronary artery disease associated with sudden cardiac death." *Heart* no. 96 (14):1119-25. doi: 10.1136/hrt.2009.185157.
- Hohnloser, S. H., K. H. Kuck, P. Dorian, R. S. Roberts, J. R. Hampton, R. Hatala, E. Fain, M. Gent, S. J. Connolly, and Dinamit Investigators. 2004. "Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction." *N Engl J Med* no. 351 (24):2481-8. doi: 10.1056/NEJMoa041489.
- Houston, BA., and M. Mukherjee. 2014 "Cardiac sarcoidosis: clinical manifestations, imaging characteristics, and therapeutic approach." *Clin Med Insights Cardiol.* no. 8 (Suppl 1):31-7.
- Huikuri, H. V., M. J. Raatikainen, R. Moerch-Joergensen, J. Hartikainen, V. Virtanen, J. Boland, O. Anttonen, N. Hoest, L. V. Boersma, E. S. Platou, M. D. Messier, P. E. Bloch-Thomsen, Arrhythmias Cardiac, and group Risk Stratification after Acute Myocardial Infarction study. 2009. "Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction." *Eur Heart J* no. 30 (6):689-98. doi: 10.1093/eurheartj/ehn537.
- Hulot, J. S., X. Jouven, J. P. Empana, R. Frank, and G. Fontaine. 2004. "Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy." *Circulation* no. 110 (14):1879-84. doi: 10.1161/01.CIR.0000143375.93288.82.
- Hulten, E., S. Aslam, M. Osborne, S. Abbasi, MS. Bittencourt, and R. Blankstein. 2016. "Cardiac sarcoidosis-state of the art review.." *Cardiovasc Diagn Ther* no. 6 (1): 50-63.
- Hundley, W. G. 2010. "The use of cardiovascular magnetic resonance to identify adverse cardiac prognosis: an important step in reducing image-related health care expenditures." *J Am Coll Cardiol* no. 56 (15):1244-6. doi: 10.1016/j.jacc.2010.07.011.
- Iles, L., H. Pfluger, A. Phrommintikul, J. Cherayath, P. Aksit, S. N. Gupta, D. M. Kaye, and A. J. Taylor. 2008. "Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping." *J Am Coll Cardiol* no. 52 (19):1574-80. doi: 10.1016/j.jacc.2008.06.049.
- Izquierdo, M., R. Ruiz-Granell, C. Bonanad, F. Chaustre, C. Gomez, A. Ferrero, P. Lopez-Lereu, J. V. Monmeneu, J. Nunez, F. J. Chorro, and V. Bodi. 2013. "Value of early cardiovascular magnetic resonance for the prediction of adverse arrhythmic cardiac events after a first noncomplicated ST-segment-elevation myocardial infarction." *Circ Cardiovasc Imaging* no. 6 (5):755-61. doi: 10.1161/CIRCIMAGING.113.000702.

- Kadish, A. H., D. Bello, J. P. Finn, R. O. Bonow, A. Schaechter, H. Subacius, C. Albert, J. P. Daubert, C. G. Fonseca, and J. J. Goldberger. 2009. "Rationale and design for the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial." *J Cardiovasc Electrophysiol* no. 20 (9):982-7. doi: 10.1111/j.1540-8167.2009.01503.x.
- Karamitsos, TD., SK. Piechnik, SM. Banyersad, M. Fontana, NB. Ntusi, M. Ferreira, CJ. Whelan, SG. Myerson, MD. Robson, PN. Hawkins, S. Neubauer, and JC. Moon. 2013. "Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis." *JACC Cardiovasc Imaging*. no. 6 (4):488-97.
- Kelle, S., S. D. Roes, C. Klein, T. Kokocinski, A. de Roos, E. Fleck, J. J. Bax, and E. Nagel. 2009. "Prognostic value of myocardial infarct size and contractile reserve using magnetic resonance imaging." *J Am Coll Cardiol* no. 54 (19):1770-7. doi: 10.1016/j.jacc.2009.07.027.
- Kellman, P., D. Hernando, and A. E. Arai. 2010. "Myocardial Fat Imaging." *Curr Cardiovasc Imaging Rep* no. 3 (2):83-91. doi: 10.1007/s12410-010-9012-1.
- Kim, R. J., D. S. Fieno, T. B. Parrish, K. Harris, E. L. Chen, O. Simonetti, J. Bundy, J. P. Finn, F. J. Klocke, and R. M. Judd. 1999. "Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function." *Circulation* no. 100 (19):1992-2002.
- Kim, S. S., S. M. Ko, S. I. Choi, B. H. Choi, and A. E. Stillman. 2016. "Sudden cardiac death from structural heart diseases in adults: imaging findings with cardiovascular computed tomography and magnetic resonance." *Int J Cardiovasc Imaging* no. 32 Suppl 1:21-43. doi: 10.1007/s10554-016-0891-3.
- Kirchhof, P., G. Breithardt, and L. Eckardt. 2006. "Primary prevention of sudden cardiac death." *Heart* no. 92 (12):1873-8. doi: 10.1136/hrt.2006.087957.
- Kirk, P., M. Roughton, JB. Porter, JM. Walker, MA. Tanner, J. Patel, D. Wu, J. Taylor, MA. Westwood, LJ. Anderson, and DJ. Pennell. 2009 "Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major." *Circulation*. no. 120 (20):1961-8.
- Kirkfeldt, R. E., J. B. Johansen, E. A. Nohr, O. D. Jorgensen, and J. C. Nielsen. 2014. "Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark." *Eur Heart J* no. 35 (18):1186-94. doi: 10.1093/eurheartj/ehf511.
- Klem, I., J. W. Weinsaft, T. D. Bahnson, D. Hegland, H. W. Kim, B. Hayes, M. A. Parker, R. M. Judd, and R. J. Kim. 2012. "Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation." *J Am Coll Cardiol* no. 60 (5):408-20. doi: 10.1016/j.jacc.2012.02.070.
- Klintschar, M., and D. Stiller. 2004. "Sudden cardiac death in hereditary hemochromatosis: an underestimated cause of death?" *Int J Legal Med*. no. 118 (3):174-7. doi: 10.1007/s00414-004-0451-6.

- Kremastinos, D., and D. Farmakis. 2011. "Iron overload cardiomyopathy in clinical practice." *Circulation*. no. 124 (20):2253-63. doi: 10.1161/CIRCULATIONAHA.111.050773.
- Kremastinos, DT., GA. Tsetsos, DP. Tsiapras, GK. Karavolias, VA. Ladis, and CA. Kattamis. 2001. "Heart failure in beta thalassemia: a 5-year follow-up study." *Am J Med*. no. 111:349-354.
- Kuck, K. H., R. Cappato, J. Siebels, and R. Ruppel. 2000. "Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH)." *Circulation* no. 102 (7):748-54.
- Kusumoto, F. M., H. Calkins, J. Boehmer, A. E. Buxton, M. K. Chung, M. R. Gold, S. H. Hohnloser, J. Indik, R. Lee, M. R. Mehra, V. Menon, R. L. Page, W. K. Shen, D. J. Slotwiner, L. W. Stevenson, P. D. Varosy, L. Welikovitsh, Society Heart Rhythm, Cardiology American College of, and Association American Heart. 2014. "HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials." *J Am Coll Cardiol* no. 64 (11):1143-77. doi: 10.1016/j.jacc.2014.04.008.
- Kwon, D. H., C. M. Halley, T. P. Carrigan, V. Zysek, Z. B. Popovic, R. Setser, P. Schoenhagen, R. C. Starling, S. D. Flamm, and M. Y. Desai. 2009. "Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study." *JACC Cardiovasc Imaging* no. 2 (1):34-44. doi: 10.1016/j.jcmg.2008.09.010.
- Kwong, R. Y., A. K. Chan, K. A. Brown, C. W. Chan, H. G. Reynolds, S. Tsang, and R. B. Davis. 2006. "Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease." *Circulation* no. 113 (23):2733-43. doi: 10.1161/CIRCULATIONAHA.105.570648.
- Larose, E., J. Rodes-Cabau, P. Pibarot, S. Rinfret, G. Proulx, C. M. Nguyen, J. P. Dery, O. Gleeton, L. Roy, B. Noel, G. Barbeau, J. Rouleau, J. R. Boudreault, M. Amyot, R. De Larochelliere, and O. F. Bertrand. 2010. "Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction traditional measures compared with microvascular obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance." *J Am Coll Cardiol* no. 55 (22):2459-69. doi: 10.1016/j.jacc.2010.02.033.
- Lee, D. C., and J. J. Goldberger. 2013. "CMR for sudden cardiac death risk stratification: are we there yet?" *JACC Cardiovasc Imaging* no. 6 (3):345-8. doi: 10.1016/j.jcmg.2012.12.006.

- Lu, M., S. Zhao, S. Jiang, G. Yin, C. Wang, Y. Zhang, Q. Liu, H. Cheng, N. Ma, T. Zhao, X. Chen, J. Huang, Y. Zou, L. Song, Z. He, J. An, J. Renate, H. Xue, and S. Shah. 2013. "Fat deposition in dilated cardiomyopathy assessed by CMR." *JACC Cardiovasc Imaging* no. 6 (8):889-98. doi: 10.1016/j.jcmg.2013.04.010.
- Lynch, JP., J. Hwang, J. Bradfield, M. Fishbein, K. Shivkumar, and R. Tung. 2014. "Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment." *Semin Respir Crit Care Med.* no. 35 (3):372-90.
- Mahrholdt, H., A. Wagner, R. M. Judd, U. Sechtem, and R. J. Kim. 2005. "Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies." *Eur Heart J* no. 26 (15):1461-74. doi: 10.1093/eurheartj/ehi258.
- Makikallio, T. H., P. Barthel, R. Schneider, A. Bauer, J. M. Tapanainen, M. P. Tulppo, G. Schmidt, and H. V. Huikuri. 2005. "Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era." *Eur Heart J* no. 26 (8):762-9. doi: 10.1093/eurheartj/ehi188.
- Mandorla, S., P.; Trambaiolo, M.; De Cristofaro, M.; Baldassi, M.; Maria Penco, and a nome del Consiglio Direttivo 2005-2007 della Società Italiana di Ecografia Cardiovascolare. "Appropriatezza dell'esame ecocardiografico e definizione delle classi di priorità: una proposta della Società Italiana di Ecografia Cardiovascolare." *G Ital Cardiol* 2010 no. 11 (6):503-533.
- Marcus, F.I., W.J. McKenna, D. Sherrill, C. Basso, B. Bauce, and D.A. Bluemke. 2010. "Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria." *Eur Heart J* no. 31:806-14.
- Maron, B. J., J. A. Towbin, G. Thiene, C. Antzelevitch, D. Corrado, D. Arnett, A. J. Moss, C. E. Seidman, J. B. Young, Association American Heart, Heart Failure Council on Clinical Cardiology, Committee Transplantation, Care Quality of, Research Outcomes, Genomics Functional, Groups Translational Biology Interdisciplinary Working, Epidemiology Council on, and Prevention. 2006. "Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention." *Circulation* no. 113 (14):1807-16. doi: 10.1161/CIRCULATIONAHA.106.174287.
- Maron, B. J., and M. S. Maron. 2013. "Hypertrophic cardiomyopathy." *Lancet* no. 381:242-255.
- Maron, M. S. 2012. "Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy." *J Cardiovasc Magn Reson* no. 14:13. doi: 10.1186/1532-429X-14-13.

- Mavrogeni, S., E. Petrou, G. Kolovou, G. Theodorakis, and E. Iliodromitis. 2013. "Prediction of ventricular arrhythmias using cardiovascular magnetic resonance." *Eur Heart J Cardiovasc Imaging* no. 14 (6):518-25. doi: 10.1093/ehjci/jes302.
- McCrohon, J. A., J. C. Moon, and S. K. Prasad. 2003. "Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance." *Circulation* no. 108:54-59.
- Meloni, A., C. Borgna-Pignatti, GC. Del Vecchio, MA. Romeo, MR. Gamberini, F. Bonetti, MG. Neri, E. Chiodi, V. Positano, and A. Pepe. 2016. "Significant improvement of survival by T2* CMR in thalassemia major." *Journal of Cardiovascular Magnetic Resonance* no. 18 (Suppl 1):P137. doi: 10.1186/1532-429X-18-S1-P137.
- Mohty, D., C. Boulogne, J. Magne, N. Varroud-Vial, S. Martin, H. Ettaif, BM. Fadel, F. Bridoux, V. Aboyans, T. Damy, and A. Jaccard. 2016. "Prognostic value of left atrial function in systemic light-chain amyloidosis: a cardiac magnetic resonance study." *Eur Heart J Cardiovasc Imaging*. no. 17 (9):961-9.
- Moretti, M., M. Merlo, G. Barbati, A. Di Lenarda, F. Brun, B. Pinamonti, D. Gregori, L. Mestroni, and G. Sinagra. 2010. "Prognostic impact of familial screening in dilated cardiomyopathy." *Eur J Heart Fail* no. 12 (9):922-7. doi: 10.1093/eurjhf/hfq093.
- Moss, A. J., H. Greenberg, R. B. Case, W. Zareba, W. J. Hall, M. W. Brown, J. P. Daubert, S. McNitt, M. L. Andrews, A. D. Elkin, and I. I. Research Group Multicenter Automatic Defibrillator Implantation Trial. 2004. "Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator." *Circulation* no. 110 (25):3760-5. doi: 10.1161/01.CIR.0000150390.04704.B7.
- Moss, A. J., W. J. Hall, D. S. Cannom, J. P. Daubert, S. L. Higgins, H. Klein, J. H. Levine, S. Saksena, A. L. Waldo, D. Wilber, M. W. Brown, and M. Heo. 1996. "Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators." *N Engl J Med* no. 335 (26):1933-40. doi: 10.1056/NEJM199612263352601.
- Moss, A. J., W. Zareba, W. J. Hall, H. Klein, D. J. Wilber, D. S. Cannom, J. P. Daubert, S. L. Higgins, M. W. Brown, M. L. Andrews, and I. I. Investigators Multicenter Automatic Defibrillator Implantation Trial. 2002. "Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction." *N Engl J Med* no. 346 (12):877-83. doi: 10.1056/NEJMoa013474.
- Myerburg, R. J., K. M. Kessler, and A. Castellanos. 1992. "Sudden cardiac death. Structure, function, and time-dependence of risk." *Circulation* no. 85 (1 Suppl):I2-10.
- Nagueh, S. F., S. M. Bierig, M. J. Budoff, M. Desai, V. Dilsizian, B. Eidem, S. A. Goldstein, J. Hung, M. S. Maron, S. R. Ommen, A. Woo, Echocardiography American Society of, Cardiology American Society of Nuclear, Resonance Society

- for Cardiovascular Magnetic, and Tomography Society of Cardiovascular Computed. 2011. "American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: Endorsed by the American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular Computed Tomography." *J Am Soc Echocardiogr* no. 24 (5):473-98. doi: 10.1016/j.echo.2011.03.006.
- Nanthakumar, K., A. E. Epstein, G. N. Kay, V. J. Plumb, and D. S. Lee. 2004. "Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials." *J Am Coll Cardiol* no. 44 (11):2166-72. doi: 10.1016/j.jacc.2004.08.054.
- Nazarian, S., D.A. Bluemke, and A.C. Lardo. 2005. "Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy." *Circulation* (112):2821-2825.
- Neilan, T. G., H. Farhad, T. Mayrhofer, R. V. Shah, J. A. Dodson, S. A. Abbasi, S. B. Danik, D. J. Verdini, M. Tokuda, U. B. Tedrow, M. Jerosch-Herold, U. Hoffmann, B. B. Ghoshhajra, W. G. Stevenson, and R. Y. Kwong. 2015. "Late gadolinium enhancement among survivors of sudden cardiac arrest." *JACC Cardiovasc Imaging* no. 8 (4):414-23. doi: 10.1016/j.jcmg.2014.11.017.
- Nijveldt, R., A. M. Beek, T. Germans, O. Bondarenko, and A. C. van Rossum. 2007. "Arrhythmogenic right ventricular cardiomyopathy with evidence of biventricular involvement." *CMAJ* no. 176 (13):1819-21. doi: 10.1503/cmaj.061626.
- Pantazis, A. A., and P. M. Elliott. 2009. "Left ventricular noncompaction." *Curr Opin Cardiol* no. 24 (3):209-13. doi: 10.1097/HCO.0b013e32832a11e7.
- Parsai, C., R. O'Hanlon, S. K. Prasad, and R. H. Mohiaddin. 2012. "Diagnostic and prognostic value of cardiovascular magnetic resonance in non-ischaemic cardiomyopathies." *J Cardiovasc Magn Reson* no. 14:54. doi: 10.1186/1532-429X-14-54.
- Patton, N., G. Brown, M. Leung, K. Bavishi, J. Taylor, J. Lloyd, S.H. Lee, L. Tay, and S. Worthley. 2010. "Observational study of iron overload as assessed by magnetic resonance imaging in an adult population of transfusion-dependent patients with beta thalassaemia: significant association between low cardiac T2* < 10 ms and cardiac events." *Intern Med J.* no. 40:419-426.
- Perez-David, E., A. Arenal, J. L. Rubio-Guivernau, R. del Castillo, L. Atea, E. Arbelo, E. Caballero, V. Celorrio, T. Datino, E. Gonzalez-Torrecilla, F. Atienza, M. J. Ledesma-Carbayo, J. Bermejo, A. Medina, and F. Fernandez-Aviles. 2011. "Noninvasive identification of ventricular tachycardia-related conducting channels using contrast-enhanced magnetic resonance imaging in patients with chronic myocardial infarction: comparison of signal intensity scar mapping and endocardial voltage mapping." *J Am Coll Cardiol* no. 57 (2):184-94. doi: 10.1016/j.jacc.2010.07.043.

- Petersen, S. E., M. Jerosch-Herold, L. E. Hudsmith, M. D. Robson, J. M. Francis, H. A. Doll, J. B. Selvanayagam, S. Neubauer, and H. Watkins. 2007. "Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging." *Circulation* no. 115 (18):2418-25. doi: 10.1161/CIRCULATIONAHA.106.657023.
- Pinto, Y. M., P. M. Elliott, E. Arbustini, Y. Adler, A. Anastakis, M. Bohm, D. Duboc, J. Gimeno, P. de Groote, M. Imazio, S. Heymans, K. Klingel, M. Komajda, G. Limongelli, A. Linhart, J. Mogensen, J. Moon, P. G. Pieper, P. M. Seferovic, S. Schueler, J. L. Zamorano, A. L. Caforio, and P. Charron. 2016. "Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases." *Eur Heart J* no. 37 (23):1850-8. doi: 10.1093/eurheartj/ehv727.
- Pontone, G., G. Di Bella, C. Silvia, V. Maestrini, P. Festa, L. Ait-Ali, P. G. Masci, L. Monti, G. di Giovine, M. De Lazzari, A. Cipriani, A. I. Guaricci, S. Dellegrottaglie, A. Pepe, M. P. Marra, and G. D. Aquaro. 2017. "Clinical recommendations of cardiac magnetic resonance, Part II: inflammatory and congenital heart disease, cardiomyopathies and cardiac tumors: a position paper of the working group 'Applicazioni della Risonanza Magnetica' of the Italian Society of Cardiology." *J Cardiovasc Med (Hagerstown)*. doi: 10.2459/JCM.0000000000000499.
- Pouleur, A. C., E. Barkoudah, H. Uno, H. Skali, P. V. Finn, S. L. Zelenkofske, Y. N. Belenkov, V. Mareev, E. J. Velazquez, J. L. Rouleau, A. P. Maggioni, L. Kober, R. M. Califf, J. J. McMurray, M. A. Pfeffer, S. D. Solomon, and Valiant Investigators. 2010. "Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both." *Circulation* no. 122 (6):597-602. doi: 10.1161/CIRCULATIONAHA.110.940619.
- Priori, S. G., C. Blomstrom-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, P. M. Elliott, D. Fitzsimons, R. Hatala, G. Hindricks, P. Kirchhof, K. Kjeldsen, K. H. Kuck, A. Hernandez-Madrid, N. Nikolaou, T. M. Norekval, C. Spaulding, and D. J. Van Veldhuisen. 2015. "2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)." *Eur Heart J* no. 36 (41):2793-867. doi: 10.1093/eurheartj/ehv316.
- Rakar, S., G. Sinagra, A. Di Lenarda, A. Poletti, R. Bussani, F. Silvestri, and F. Camerini. 1997. "Epidemiology of dilated cardiomyopathy. A prospective post-mortem study of 5252 necropsies. The Heart Muscle Disease Study Group." *Eur Heart J* no. 18 (1):117-23.

- Reant, P., G. Captur, M. Mirabel, A. Nasis, M. Sado D, V. Maestrini, S. Castelletti, C. Manisty, A. S. Herrey, P. Syrris, M. Tome-Esteban, S. Jenkins, P. M. Elliott, W. J. McKenna, and J. C. Moon. 2015. "Abnormal septal convexity into the left ventricle occurs in subclinical hypertrophic cardiomyopathy." *J Cardiovasc Magn Reson* no. 17:64. doi: 10.1186/s12968-015-0160-y.
- Reichek, N., and D. Gupta. 2008. "Hypertrophic cardiomyopathy: cardiac magnetic resonance imaging changes the paradigm." *J Am Coll Cardiol* no. 52 (7):567-8. doi: 10.1016/j.jacc.2008.05.014.
- Rigato, I., B. Bauce, A. Rampazzo, A. Zorzi, K. Pilichou, E. Mazzotti, F. Migliore, M. P. Marra, A. Lorenzon, M. De Bortoli, M. Calore, A. Nava, L. Daliento, D. Gregori, S. Illiceto, G. Thiene, C. Basso, and D. Corrado. 2013. "Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy." *Circ Cardiovasc Genet* no. 6 (6):533-42. doi: 10.1161/CIRCGENETICS.113.000288.
- Roes, S. D., C. J. Borleffs, R. J. van der Geest, J. J. Westenberg, N. A. Marsan, T. A. Kaandorp, J. H. Reiber, K. Zeppenfeld, H. J. Lamb, A. de Roos, M. J. Schalij, and J. J. Bax. 2009. "Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator." *Circ Cardiovasc Imaging* no. 2 (3):183-90. doi: 10.1161/CIRCIMAGING.108.826529.
- Roes, S. D., S. Kelle, T. A. Kaandorp, T. Kokocinski, D. Poldermans, H. J. Lamb, E. Boersma, E. E. van der Wall, E. Fleck, A. de Roos, E. Nagel, and J. J. Bax. 2007. "Comparison of myocardial infarct size assessed with contrast-enhanced magnetic resonance imaging and left ventricular function and volumes to predict mortality in patients with healed myocardial infarction." *Am J Cardiol* no. 100 (6):930-6. doi: 10.1016/j.amjcard.2007.04.029.
- Sado, D. M., S. K. White, S. K. Piechnik, S. M. Banypersad, T. Treibel, G. Captur, M. Fontana, V. Maestrini, A. S. Flett, M. D. Robson, R. H. Lachmann, E. Murphy, A. Mehta, D. Hughes, S. Neubauer, P. M. Elliott, and J. C. Moon. 2013. "Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping." *Circ Cardiovasc Imaging* no. 6 (3):392-8. doi: 10.1161/CIRCIMAGING.112.000070.
- Schelbert, E. B., J. J. Cao, S. Sigurdsson, T. Aspelund, P. Kellman, A. H. Aletras, C. K. Dyke, G. Thorgeirsson, G. Eiriksdottir, L. J. Launer, V. Gudnason, T. B. Harris, and A. E. Arai. 2012. "Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults." *JAMA* no. 308 (9):890-6. doi: 10.1001/2012.jama.11089.
- Schinkel, A. F. 2013. "Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and

- inappropriate interventions, and complications.” *Circ Arrhythm Electrophysiol* no. 6 (3):562-8. doi: 10.1161/CIRCEP.113.000392.
- Schinkel, A. F., D. Poldermans, A. Elhendy, and J. J. Bax. 2006. “Prognostic role of dobutamine stress echocardiography in myocardial viability.” *Curr Opin Cardiol* no. 21 (5):443-9. doi: 10.1097/01.hco.0000240580.82182.05.
- Schmidt, A., C. F. Azevedo, A. Cheng, S. N. Gupta, D. A. Bluemke, T. K. Foo, G. Gerstenblith, R. G. Weiss, E. Marban, G. F. Tomaselli, J. A. Lima, and K. C. Wu. 2007. “Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction.” *Circulation* no. 115 (15):2006-14. doi: 10.1161/CIRCULATIONAHA.106.653568.
- Schuleri, K. H., M. Centola, K. S. Evers, A. Zviman, R. Evers, J. A. Lima, and A. C. Lardo. 2012. “Cardiovascular magnetic resonance characterization of peri-infarct zone remodeling following myocardial infarction.” *J Cardiovasc Magn Reson* no. 14:24. doi: 10.1186/1532-429X-14-24.
- Scott, P. A., J. M. Morgan, N. Carroll, D. C. Murday, P. R. Roberts, C. R. Peebles, S. P. Harden, and N. P. Curzen. 2011. “The extent of left ventricular scar quantified by late gadolinium enhancement MRI is associated with spontaneous ventricular arrhythmias in patients with coronary artery disease and implantable cardioverter-defibrillators.” *Circ Arrhythm Electrophysiol* no. 4 (3):324-30. doi: 10.1161/CIRCEP.110.959544.
- Scott, P. A., J. A. Rosengarten, N. P. Curzen, and J. M. Morgan. 2013. “Late gadolinium enhancement cardiac magnetic resonance imaging for the prediction of ventricular tachyarrhythmic events: a meta-analysis.” *Eur J Heart Fail* no. 15 (9):1019-27. doi: 10.1093/eurjhf/hft053.
- Scott, P. A., J. A. Rosengarten, A. Shahed, A. M. Yue, D. C. Murday, P. R. Roberts, C. R. Peebles, S. P. Harden, N. P. Curzen, and J. M. Morgan. 2013. “The relationship between left ventricular scar and ventricular repolarization in patients with coronary artery disease: insights from late gadolinium enhancement magnetic resonance imaging.” *Europace* no. 15 (6):899-906. doi: 10.1093/europace/eus362.
- Sen-Chowdhry, S., P. Syrris, and W. J. McKenna. 2010. “Genetics of restrictive cardiomyopathy.” *Heart Fail Clin* no. 6 (2):179-86. doi: 10.1016/j.hfc.2009.11.005.
- Sen-Chowdhry, S., P. Syrris, and D. Ward. 2007. “Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression.” *Circulation* (115):1710-1720.
- Smith, T., L. Jordaens, D. A. Theuns, P. F. van Dessel, A. A. Wilde, and M. G. Hunink. 2013. “The cost-effectiveness of primary prophylactic implantable defibrillator therapy in patients with ischaemic or non-ischaemic heart disease: a European analysis.” *Eur Heart J* no. 34 (3):211-9. doi: 10.1093/eurheartj/ehs090.
- Solomon, S. D., S. Zelenkofske, J. J. McMurray, P. V. Finn, E. Velazquez, G. Ertl, A. Harsanyi, J. L. Rouleau, A. Maggioni, L. Kober, H. White, F. Van de Werf, K.

- Pieper, R. M. Califf, M. A. Pfeffer, and Investigators Valsartan in Acute Myocardial Infarction Trial. 2005. "Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both." *N Engl J Med* no. 352 (25):2581-8. doi: 10.1056/NEJMoa043938.
- Stecker, E. C., C. Vickers, J. Waltz, C. Socoteanu, B. T. John, R. Mariani, J. H. McAnulty, K. Gunson, J. Jui, and S. S. Chugh. 2006. "Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study." *J Am Coll Cardiol* no. 47 (6):1161-6. doi: 10.1016/j.jacc.2005.11.045.
- Steinbeck, G., D. Andresen, K. Seidl, J. Brachmann, E. Hoffmann, D. Wojciechowski, Z. Kornacewicz-Jach, B. Sredniawa, G. Lupkovics, F. Hofgartner, A. Lubinski, M. Rosenqvist, A. Habets, K. Wegscheider, J. Senges, and Iris Investigators. 2009. "Defibrillator implantation early after myocardial infarction." *N Engl J Med* no. 361 (15):1427-36. doi: 10.1056/NEJMoa0901889.
- Syed, IS., JF. Glockner, D. Feng, PA. Araoz, MW. Martinez, Edwards WD., MA. Gertz, A. Dispenzieri, JK. Oh, and D. Bellavia. 2010. "Role of Cardiac Magnetic Resonance Imaging in the Detection of Cardiac Amyloidosis." *JACC: Cardiovascular Imaging* no. 3 (2):155-164.
- Takahashi, T., P. van Dessel, J. C. Lopshire, W. J. Groh, J. Miller, J. Wu, and D. P. Zipes. 2004. "Optical mapping of the functional reentrant circuit of ventricular tachycardia in acute myocardial infarction." *Heart Rhythm* no. 1 (4):451-9. doi: 10.1016/j.hrthm.2004.05.005.
- Tanner, MA., R. Galanello, C. Dessi, MA. Westwood, GC. Smith, SV. Nair, LJ. Anderson, JM. Walker, and DJ. Pennell. 2006. "Myocardial iron loading in patients with thalassemia major on deferoxamine chelation." *J Cardiovasc Magn Reson.* no. 8:543-547.
- Taylor, M. R., P. R. Fain, G. Sinagra, M. L. Robinson, A. D. Robertson, E. Carniel, A. Di Lenarda, T. J. Bohlmeier, D. A. Ferguson, G. L. Brodsky, M. M. Boucek, J. Lascor, A.C. Moss, W.L. Li, G.L. Stetler, F. Muntoni, M.R. Bristow, and L. Mestroni. 2003. "Natural history of dilated cardiomyopathy due to lamin A/C gene mutations." *J Am Coll Cardiol*:771-780.
- Todiare, G., L. Piscicella, A. Barison, A. Del Franco, E. Zachara, P. Piaggi, F. Re, A. Pingitore, M. Emdin, M. Lombardi, and G. D. Aquaro. 2014. "Abnormal T2-STIR magnetic resonance in hypertrophic cardiomyopathy: a marker of advanced disease and electrical myocardial instability." *PLoS One* no. 9 (10):e111366. doi: 10.1371/journal.pone.0111366.
- Tung, R., and C. D. Swerdlow. 2009. "Refining patient selection for primary prevention implantable cardioverter-defibrillator therapy: reeling in a net cast too widely." *Circulation* no. 120 (10):825-7. doi: 10.1161/CIRCULATIONAHA.109.891069.

- Tung, R., P. Zimetbaum, and M. E. Josephson. 2008. "A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death." *J Am Coll Cardiol* no. 52 (14):1111-21. doi: 10.1016/j.jacc.2008.05.058.
- Van der Wall, E. E., H. W. Kayser, M. M. Bootsma, A. de Roos, and M. J. Schalij. 2000. "Arrhythmogenic right ventricular dysplasia: MRI findings." *Herz* no. 25 (4):356-64.
- Van Welsenes, G. H., J. B. van Rees, C. J. Borleffs, S. C. Cannegieter, J. J. Bax, L. van Erven, and M. J. Schalij. 2011. "Long-term follow-up of primary and secondary prevention implantable cardioverter defibrillator patients." *Europace* no. 13 (3):389-94. doi: 10.1093/europace/euq494.
- Watkins, H., H. Ashrafian, and W. J. McKenna. 2008. "The genetics of hypertrophic cardiomyopathy: Teare redux." *Heart* no. 94 (10):1264-8. doi: 10.1136/hrt.2008.154104.
- Weiss, J. P., O. Saynina, K. M. McDonald, M. B. McClellan, and M. A. Hlatky. 2002. "Effectiveness and cost-effectiveness of implantable cardioverter defibrillators in the treatment of ventricular arrhythmias among medicare beneficiaries." *Am J Med* no. 112 (7):519-27.
- Wellens, H. J., P. J. Schwartz, F. W. Lindemans, A. E. Buxton, J. J. Goldberger, S. H. Hohnloser, H. V. Huikuri, S. Kaab, M. T. La Rovere, M. Malik, R. J. Myerburg, M. L. Simoons, K. Swedberg, J. Tijssen, A. A. Voors, and A. A. Wilde. 2014. "Risk stratification for sudden cardiac death: current status and challenges for the future." *Eur Heart J* no. 35 (25):1642-51. doi: 10.1093/eurheartj/ehu176.
- Weng, Z., J. Yao, R. H. Chan, J. He, X. Yang, Y. Zhou, and Y. He. 2016. "Prognostic Value of LGE-CMR in HCM: A Meta-Analysis." *JACC Cardiovasc Imaging* no. 9 (12):1392-1402. doi: 10.1016/j.jcmg.2016.02.031.
- White, J. A., N. M. Fine, L. Gula, R. Yee, A. Skanes, G. Klein, P. Leong-Sit, H. Warren, T. Thompson, M. Drangova, and A. Krahn. 2012. "Utility of cardiovascular magnetic resonance in identifying substrate for malignant ventricular arrhythmias." *Circ Cardiovasc Imaging* no. 5 (1):12-20. doi: 10.1161/CIRCIMAGING.111.966085.
- Wolf, J.E., L. Rose-Pittet, and E. Page. 1989. "Detection of parietal lesions using magnetic resonance imaging in arrhythmogenic dysplasia of the right ventricle." *Arch Mal Coeur Vaiss* no. 82:1711-1717.
- Wu, E., R. M. Judd, J. D. Vargas, F. J. Klocke, R. O. Bonow, and R. J. Kim. 2001. "Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction." *Lancet* no. 357 (9249):21-8. doi: 10.1016/S0140-6736(00)03567-4.
- Wu, K. C. 2012. "Assessing risk for ventricular tachyarrhythmias and sudden cardiac death: is there a role for cardiac MRI?" *Circ Cardiovasc Imaging* no. 5 (1):2-5. doi: 10.1161/CIRCIMAGING.111.971135.
- Yan, A. T., A. J. Shayne, K. A. Brown, S. N. Gupta, C. W. Chan, T. M. Luu, M. F. Di Carli, H. G. Reynolds, W. G. Stevenson, and R. Y. Kwong. 2006. "Characterization

- of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality.” *Circulation* no. 114 (1):32-9. doi: 10.1161/CIRCULATIONAHA.106.613414.
- Zaman, S., and P. Kovoov. 2014. “Sudden cardiac death early after myocardial infarction: pathogenesis, risk stratification, and primary prevention.” *Circulation* no. 129 (23):2426-35. doi: 10.1161/CIRCULATIONAHA.113.007497.
- Zecchin, M., M. Merlo, and A. Pivetta. 2012. “How can optimization of medical treatment avoid unnecessary implantable cardioverter-defibrillator implantations in patients with idiopathic dilated cardiomyopathy presenting with “SCD-HeFT criteria?”” *Am J Cardiol*:729–735.
- Zeidan-Shwiri, T., D. Aronson, K. Atalla, M. Blich, M. Suleiman, I. Marai, L. Gepstein, L. Lavie, P. Lavie, and M. Boulos. 2011. “Circadian pattern of life-threatening ventricular arrhythmia in patients with sleep-disordered breathing and implantable cardioverter-defibrillators.” *Heart Rhythm* no. 8 (5):657-62. doi: 10.1016/j.hrthm.2010.12.030.
- Zipes, D. P., and H. J. Wellens. 1998. “Sudden cardiac death.” *Circulation* no. 98 (21):2334-51.

Chapter 10

CANCER TREATMENT AND THE RISK OF SUDDEN CARDIAC DEATH

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ABSTRACT

Patients with Cancer who were treated with Cancer therapies can reach to a survival rate of 90%, and females with Breast malignancies are good example of this success. The Cancer therapies can be in the form of the classical chemotherapy such as anthracyclines, the newly targeted therapies like VEGF inhibitors, Radiotherapy, or a combination of treatments.

All these medications, in spite of their effectiveness in halting and/or damaging Cancer tissues, they express a collateral insult on the Cardiovascular System leading to the uprising of different life threatening pathologies. This new challenge taking place in the post-Cancer period is known as Cardiotoxicity and led to the emerging of the new science known as Cardio-Oncology.

One of the most aggressive Cardiotoxic out comes is the development of Sudden Cardiac Death. This fatal pathology can take place at any level of Cancer therapy and may end up with losing the patients who are under treatment.

Attending Physicians, either Cardiologists or Oncologists, should be aware of the detailed adverse side effects of Cancer therapies to avoid easy losing of their patients.

To our knowledge there is no studies performed before covering the Sudden Cardiac Death per se during the treatment of Cancer and we hope that the future studies will explore this important issue. We will try to present data from the scarce pool of the Cardio-Oncology literature, position papers, and Guidelines that dealt with Sudden Cardiac Death.

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Conclusion: Sudden Cardiac Death should be an expected outcome when some types of therapies are applied to Cancer patients in the form of Chemotherapy, Radiotherapy or both and may lead to increased morbidity and mortality.

Keywords: sudden cardiac death SCD, cardio-oncology, arrhythmias, chemotherapy, radiotherapy, cardiotoxicity, cardiomyopathy

ABBREVIATIONS

SCD	Sudden Cardiac Death
TdP	Torsade de Pointes
5FU	5 Fluorouracil
TLS	Tumor Lysis Syndrome
LAA	Left Atrial Appendage
DVT	Deep Vein Thrombosis
LMWH	Low Molecular Weight Heparin
ATEs	Arterial Thrombotic events
CAD	Coronary Artery Disease
ACS	Acute Coronary Syndrome
MI	Myocardial Infarction
PE	Pulmonary Embolism
AF	Atrial Fibrillation

INTRODUCTION

Patients with Cancer who were treated with Cancer therapies can reach to a survival rate of 90%, and females with Breast malignancies are good example of this success. The Cancer therapies can be in the form of the classical chemotherapy such as anthracyclines, the newly targeted therapies like VEGF inhibitors, Radiotherapy, or a combination of treatments (Committee opinion no. 606-2014).

The successful treatment and control of Cancer by the physicians, and the good response from the patients will lead to a longer survival rate. But unfortunately these patients are facing a serious threat to their lives in the form of newly established Cardiovascular Diseases and eventually presenting with several complications, the most dangerous of all is the Sudden Cardiac Death (Di Francia and colleagues 2017 Feb 8) see also (Figure 1).



Based on data from SEER 18 2006-2012. Gray figures represent those who have died from female breast cancer. Green figures represent those who have survived 5 years or more.

Figure 1. Percent surviving 5 years from Breast Cancer = 89.7%.

The survival statistics are usually based on studying large groups of patients and they cannot be used to predict exactly what will happen to an individual patient. We believe in the fact that there are no two patients who are entirely alike even in the responses to treatment. For these reasons, a new science had to be created in the field of Cardiology, called the Cardio-Oncology or Onco-Cardiology which is dealing with Cancer patients in an individualized manner before starting the treatment, throughout their treatment period, and even long time after termination of treatment sessions trying to prevent, minimize or cure the cardiotoxicity effects in these fragile patients.

The most studied chemotherapy is the anthracycline group where about 2.2% of patients on these drugs develop signs and symptoms of heart failure (Von Hoff DD and colleagues 1979). Also 65% of patients with history of childhood malignancies are treated with doxorubicin, which is an important anthracycline and commonly used in the treatment of different Cancers, and can present to us as at least an echocardiographic full picture of Left ventricular dysfunction in their adulthood period (Grenier MA and Lipshultz SE 1998). The 2012 meta-analysis by Moja and colleagues of over 10,000 patients included in this trial indicated that these patients have a risk ratio (RR) for Congestive Heart Failure (which is an indirect cause of Sudden Cardiac Death) of 5.11 [95% confidence interval (CI) 3.00-8.72, $p < 0.0001$] when using trastuzumab (a targeted chemotherapy and causing type 2 toxicity) as a treatment compared with controls (Moja L and colleagues) (The committee opinion no. 606-2014).

In this chapter we will not deal with the whole topic of Cardiotoxicity which is involving a wide spectrum of Cancer treatments and creating a large sum of complications, but we will consider only Cardiotoxic therapies which are enhancing the development of Sudden Cardiac Death. The SCD as an event causes the loss of the patients' lives all of a sudden, and even if they are successfully resuscitated, it will leave these patients in a state of a very high risk of possible Sudden Cardiac Arrest recurrence when these therapies are used again.

The prevalence of SCD out of all Cancer patients deaths is about 4%, and 90% of these Sudden Deaths are due to Coronary Heart Disease (ESC CPG position paper 2016). This gives us the hint that Cancer therapies are precipitating ischemia and atherosclerosis by away or another in some of the Cancer treated patients (depending on several factors).

In general, when we talk about Sudden Cardiac Death we mean a death due to Arrhythmias which directly and immediately may trigger sudden arrest of the heart, especially when the Ventricular Arrhythmias are formed. We will include in our talk the important pathologies that are “leading to and ending by” Arrhythmias and Sudden Death and that are caused by Cancer treatment directly or indirectly and this will include a wide range of pathologies that we will try to cover them as much as this chapter allow and concentrate on the important and commonly seen ones in our clinical practice.

DEFINITION OF THE SCD

We will be referring here to the definition(s) which were agreed and approved by the European Society Of Cardiology in its published Guidelines for the Ventricular Arrhythmias and Sudden Cardiac Death for the year 2015 (Mazzanti A 2015).

Sudden Death = is defined as a Non-Traumatic and Unexpected fatal event occurring within one hour of the onset of symptoms in apparently healthy objects. If death is not witnessed, the definition applies when the victim was in good health 24 hours before the event (Mazzanti A 2015).

The term *Sudden Cardiac Death* is used when:

- Acquired or Congenital, potentially fatal Cardiac condition was known to be present during life. OR
- Autopsy has identified a Cardiac or Vascular anomaly as the possible cause of the event. OR
- No obvious extra Cardiac cause have been identified by Post-Mortem examination and therefore an arrhythmic event is a likely cause of death (Mazzanti A 2015).

CAUSES OF SCD IN CANCER PATIENTS

(DI MAIO 1980) (INAGAKI 1974)

- Direct Cancer involvement to the heart.
- Treatment of Cancer and the development of Sudden Cardiac Death.

- Other mechanisms not related to Cancer.

We will deal in this Chapter with SCD caused by Cancer treatment in particular and we will be reviewing in brief about the other important causes.

CLASSIFICATION OF CARDIAC TOXICITY CAUSING SCD

(DI MAIO 1980) (INAGAKI 1974) (KUFE DW)

Classifications vary with different Guidelines, but here we will use the easier ones from the literature:

1. Toxicity Causing a Direct SCD (i.e Arrhythmias)

Here the SCD is happening all of a sudden during the treatment of Cancer, and if the patients are asymptomatic, the cause of cardiac death may be underdiagnosed by the attending physician, unless he/she is fully aware of the treatment adverse effects, can predict the toxicity and ready to manage them in proper time. Usually the cause of this type is Ventricular Arrhythmia.

2. Toxicity Ending into SCD (i.e CHD, Heart Failure, Etc.)

In this type of toxicity the patient passes first by different pathologies ending with SCD, and here we usually can expect the SCD and we have the chance to do the needed efforts to avoid the cardiac arrest and prepare ourselves to manage it when it takes place.

CHEMOTHERAPY AND SUDDEN CARDIAC DEATH (SCD)

Chemotherapy is the main treatment for different Cancers and they cause the development of SCD by inducing the following main pathological conditions (ESC CPG position paper 2016):

1. Angina

A very important sign that should be aware of by the attending physicians and rings the bell to intervene with the patient since this sign may indicate the presence of Ischemic

Heart Disease, either present from the start or induced by the Cancer treatment. This important sign can alert us to introduce the needed preventive measures for SCD in the proper time.

2. Acute Coronary Syndrome (MI)

This can be induced by the chemotherapy at the start of treatment of Cancer or delayed for some time in the form of Progressive Coronary Atherosclerosis or other mechanisms. Full Guidelines management of Acute Coronary Syndrome should be applied. Sudden Cardiac Death, as we all know, is an expected outcome of Myocardial Infarction.

3. Congestive Heart Failure

This is the typical end result for most of Cancer treatments. Proper treatment should be done according to Guidelines of Management and Treatment of Acute and Chronic Heart Failure (ESC Guidelines 2012, 2016).

4. Thrombosis and Pulmonary Embolism

Cancer treatment can cause the deterioration of the already present pro-coagulation state (induced by Cancer itself) or start it de novo leading to different states of thrombosis and may lead to a Pulmonary Embolism and eventually into Sudden Cardiac Death. Effective and in time diagnosis and treatment are highly recommended in this condition.

5. Arrhythmias

Different Arrhythmias Can be initiated by several therapies of Cancer either direct or through certain pathological changes that end up with arrhythmias. This is one of the nastiest causes of rapid and sudden loss of lives. Proper aware and in time management are required.

The details of the above conditions will be explained in more details below.

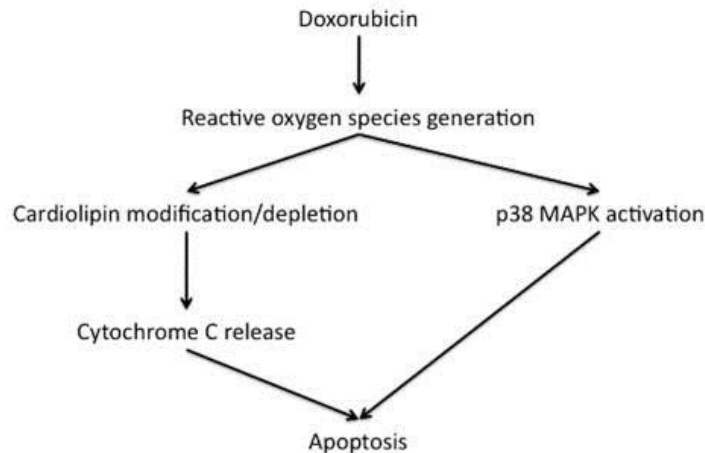


Figure 2. Cellular mechanisms responsible for increased apoptosis in cardiac myocytes by doxorubicin. *Curr. Cardiol. Rev.* 2011 Nov; 7(4): 214-220.

THE MAIN DRUGS USED TO TREAT CANCER AND CAUSE SUDDEN CARDIAC DEATH

1. Anthracyclines

Anthracyclines: (ESC CPG position paper 2016) (Cardinal D 2016) (Rabkin SW1987) (Yeh ET 2004) (Volkova M 2011).

Anthracyclines are the classically used chemotherapies, their toxicity is a dose dependent, and the examples of this group are *doxorubicin*, *daunorubicin*, *idarubicin*, *Epirubicin*. Their toxicity is called type I toxicity and usually irreversible. 1% of patients receiving Doxorubicin are reported to develop Sudden Cardiac Death. Also 30% of patients receiving doxorubicin are reported to develop Electrocardiographic (ECG) changes and Rhythm abnormalities.

Mitoxantrone and *mitomycin* are other examples of this important group of medications. The incidence of toxicity in this group of drugs ranges from 0.2%-30% depending on type of the drug and the mode of administration.

The heart, in particular, is susceptible to anthracycline-induced damage, in part, owing to anthracyclines' high affinity for Cardiocalin Figure 2. Cardiocalin is a unique mitochondrial phospholipid involved in various stages of mitochondrial membrane dynamics and the mitochondrial apoptotic process. During the initial stages of apoptosis, seemingly in coordination with death receptor stimulation and the generation of reactive oxygen species (ROS), Cardiocalin can become peroxidized. Peroxidation of Cardiocalin

can interfere with the localization of heme iron of cytochrome C and cause its release, as well as the release of additional apoptogenic factors, from mitochondria. While it appears that peroxidation of Cardiolipin plays a critical role in releasing cytochrome C from the inner mitochondrial membrane, cytochrome C itself can catalyze Cardiolipin peroxidation. Cardiolipin's cellular role is multifaceted and further investigation into its contribution to apoptosis is warranted (Danielle Harake 2012).

One of the mechanisms of SCD with anthracyclines treatment, that it may cause severe Left Ventricular Systolic Dysfunction (Figure 4) and heart failure which may progress and end up with Sudden Cardiac Death. This Left Ventricular Dysfunction may be due to the induction of oxidative stress and free radical release, inducing direct damage to the heart muscle cells (Figure 3). Other suggestions are focal fibrosis, increased wall stress and drop out of cardiac muscle cells ending into a dilated cardiomyopathy.

Anthracyclines have the efficacy to treat Solid Tumors and Hematological Malignancies. If avoided, they put a negative impact on prognosis of these Cancer patients. They should be continued, but with the proper follow up by the joint efforts of the Cardiologists and Oncologists and may need the assistance of the Hematologists and Nephrologists (what is called now the Ideal Cardio-Oncology Clinics) (Danielle Harake 2012).

The Acute stage of toxicity by anthracyclines usually associated with Supraventricular Arrhythmias. Late stage toxicity will bring the patient into the Left Ventricular Dysfunction and Heart Failure and both conditions (acute and late) are good substrates for the Sudden Cardiac Death.

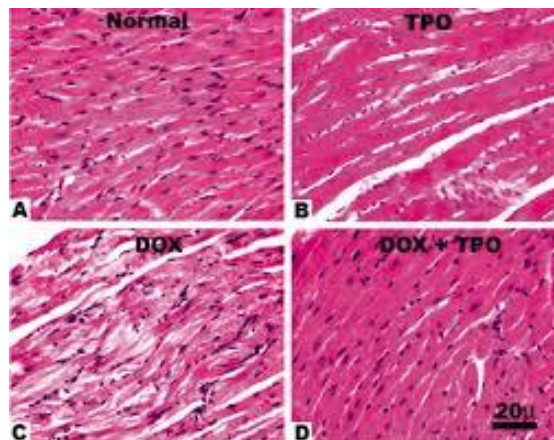


Figure 3. *Anthracyclines* Histopathological changes in the Cardiotoxic Heart.

2. Cyclophosphamides (ESC CPG Position Paper 2016)

The Cardiotoxicity of cyclophosphamide is initiated mostly with high doses of the drug (>140 mg/kg) with an obvious non-cumulative toxicity manner, or during rapid intravenous infusion, and can cause Ventricular Arrhythmias, Cardiomyopathies with Hemorrhagic Myocarditis and Pericardial Effusion and ending up with Sudden Cardiac Death. The incidence of Cardiotoxicity ranges between 7%-28%. The precise mechanism of cyclophosphamide-induced cardiac toxicity has not been well established yet. Suggestions are assuming that Cyclophosphamide metabolites cause an oxidative stress and direct endothelial capillary damage with resultant extravasation of proteins, erythrocytes, and toxic metabolites (Figure 5) (Sumandeep 2013). Breakdown of the endothelial cells in the presence of toxic metabolites causes direct damage to the myocardium and capillary blood vessels resulting in edema, interstitial hemorrhage, and formation of micro thrombi. These insults manifest clinically as an Acute Heart Failure and Arrhythmias. The latter two pathologies are well-known causes of Sudden Cardiac Death.

In general the Cardiotoxicity is uncommon but can happen at any time especially if the patient had previously received anthracyclines or underwent Radiotherapy, and here the side effects should be well expected by the treating physician and be prepared to manage them properly (Figure 5).

By Echocardiography we can notice different levels of changes, but in severe form we may find severe thickening of the myocardium, a significant pericardial effusion, and an evidence of tamponade with right ventricular diastolic collapse and marked variation of Right Ventricular Outflow during respiration (Figure 5) (Sumandeep 2013).

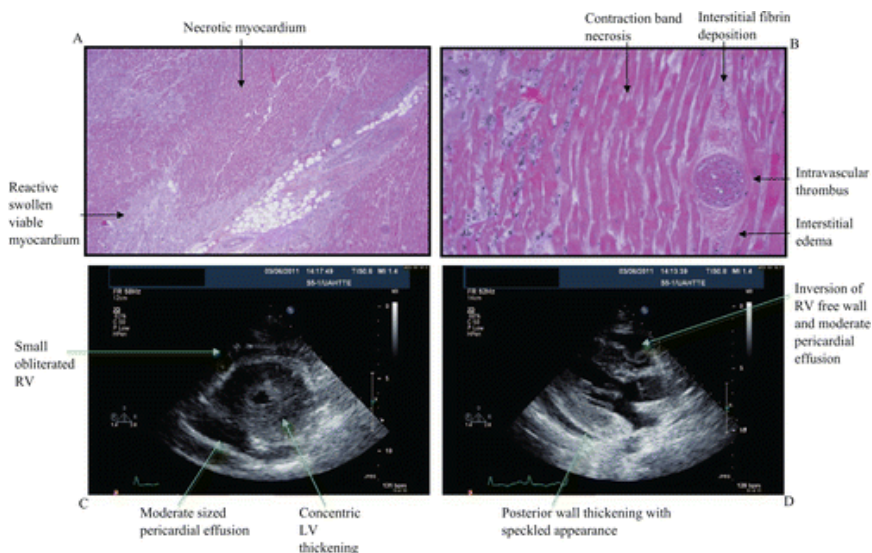


Figure 5. Pathologic and echocardiographic manifestations of cyclophosphamide-induced cardiac toxicity.

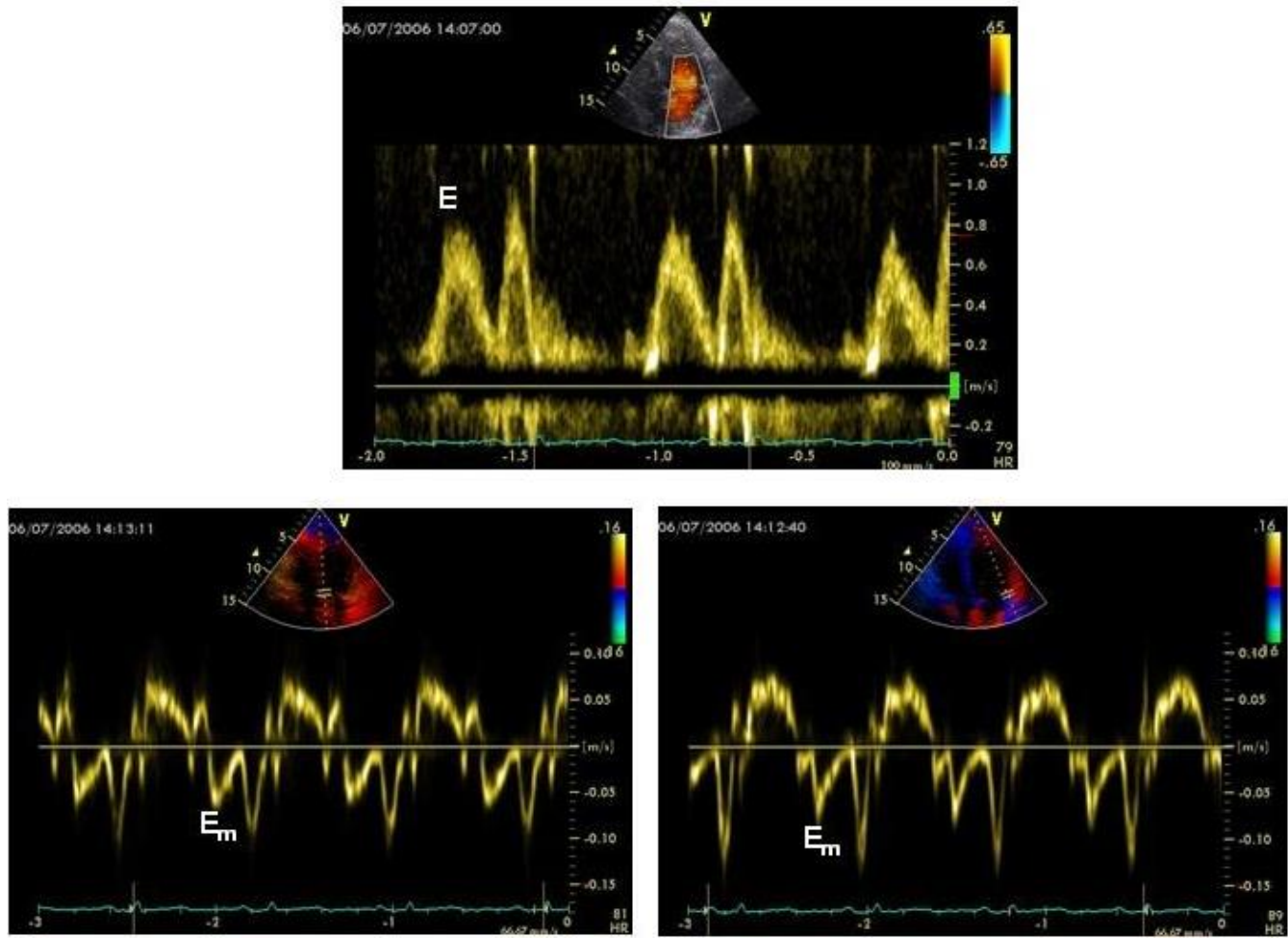


Figure 4. Doppler and tissue Doppler Changes in the anthracycline toxicity of the Heart.

Cyclophosphamide as a chemotherapy is used to treat lymphoma, multiple myeloma, leukemia, ovarian cancer, breast cancer, small cell lung cancer, bladder cancer, myeloproliferative disorders and sarcoma.

3. Fluoropyrimidines

They are commonly used Antimetabolites in the treatment of Cancer. The typical example is the 5 *fluorouracil* (5FU) and its oral form *capecitabine*.

Cardiotoxicity typically occurs with early onset (within 2-5 days of starting therapy) and in high doses of 600-1000 mg/m²/day, but any dose can initiate this toxicity.

These drugs are commonly used in the treatment of Gastro-Intestinal Cancers (advanced Colon Cancer, Anal Cancer, Pancreatic Cancer and Hepato-Biliary Cancer).

They mainly cause Vasospasm of the Coronaries, even in non-ischemic patients and ending up with Angina, Ischemia, Acute Coronary Syndrome, Cardiogenic Shock and Sudden Cardiac Death (Shoemaker 2004).

The frequency of Cardiac Events including Acute Coronary Syndrome is 7.6%, with mortality rate is 2.2% during the continuous 5FU infusion. The total incidence of toxicity can reach up to 20%. Etiology is not known but may be due to Endothelial Injury and Vasospasm, other suggestions are Coronary Artery Thrombosis or Arteritis secondary to drug exposure. The main challenge in these patients is that about 7% have Silent Ischemia, and Sudden Cardiac Death can take place without any signs or symptoms.

Usually there is a typical chest pain (Angina) and ECG changes (68% of patients) at rest and less with effort (Shoemaker 2004).

It is not unusual to lose patients while they are on treatment with these medications due to precipitation of ischemia, and not infrequently this is attributed by mistake to Cancer fatal outcome, especially in patients with no history of Coronary Heart Disease. If the Patient has a well-documented history of Coronary Heart Disease or risk factors, he/she should be well evaluated and managed before treatment with this class of anti-cancer.

4. Cytokines and Monoclonal Antibodies

Interleukin-2 and interferon-alpha are examples of Cytokines and the VSP inhibitors are an example of Monoclonal antibodies. They cause Sudden Cardiac Death by inducing severe hypotension and arrhythmias. An increased risk for Arterial Thromboembolic events (ATEs) has been linked to the use of bevacizumab and ramucirumab (Abdel-Qadir 2017) the overall incidence of bevacizumab-induced thromboembolism is about 21% (grades 3/4: 15%) and consists of Venous Thromboembolism (all-grade: 8%; grades 3/4:

5% to 7%) and Arterial Thrombosis (all-grade: 6%; grades 3/4: 3%). In a pooled analysis of 1,745 patients, of whom 963 were treated with bevacizumab (24% breast cancer), the incidence of thromboembolic events were 4% in patients treated with bevacizumab plus chemotherapy, and 2% in those treated with chemotherapy alone. Ramucirumab-induced Arterial Thrombosis (including Myocardial Infarction, Cardiac Arrest, Cerebrovascular Accident, and Cerebral Ischemia) was seen in 2% of Cancer patients (Abdel-Qadir 2017).

Pathologically it is suggested that they induce Endothelial Dysfunction and Injury. Arterial Thrombosis including that of the Coronaries is a sort of mechanism by which these patients develop Acute Coronary Syndrome and Sudden Cardiac Death (ESC CPG position paper 2016).

5. Inhibitors of Microtubule Polymerization

Paclitaxel administered as a chemotherapy can be associated with Myocardial Ischemia and the development of Myocardial Infarction and Sudden Cardiac Death. The manifestation of this Cardiac Ischemia is reported in 5% of patients using this drug (The committee opinion no. 606-2014). Beside the initiation of Myocardial Ischemia, Paclitaxel can induce Ventricular Arrhythmias, Bradycardia and several degrees of A-V blocks. The combination of doxorubicin and Paclitaxel can result in a very high cardiotoxic results and the combination should be avoided as much as possible.

6. Novel Cancer Therapies

The new Immune therapies such as Immune Check Point Inhibitors like *CTLA4*, *PDI*, *PD-L1 inhibitors* are used in the treatment of highly resistant tumors such as metastatic Melanomas and can precipitate an Autoimmune Dilated Cardiomyopathy and the development of Sudden Cardiac Death.

Also *Androgen deprivation therapy* is another class of Cancer treatments that causes acceleration of atherosclerosis, initiate Insulin Resistance, Obesity, Metabolic Syndrome, MI, and Sudden Cardiac Death. These side effects are due to the suppression of Androgens.

A. Radiotherapy and Sudden Cardiac Death

Irradiation of the heart to a sufficiently high doses can damage any component of the heart, including pericardium, myocardium, heart valves, coronary arteries, capillaries, and the conducting system. For instance acute pericarditis can take place rapidly in the course of the Radiotherapy to the chest. This can lead to Pericardial Effusion, Tamponade

and Pericardial Fibrosis (seen as an Echocardiography changes) and lead to a hemodynamic compromise that may induce a Sudden Cardiac Death.

Also direct Radiotherapy to the heart can lead to different conduction abnormalities, T wave changes and arrhythmias (seen as an ECG changes).

Radiotherapy can lead to accelerated sclerosis with Coronary Artery Endarteritis, medial layer fibrosis, intimal proliferation ending up in Acute Coronary Syndrome and Sudden Cardiac Death. The Radiotherapy applied to the heart region during treatment of Cancer can accelerate the atherosclerosis process and complicated by plaque rupture, thrombosis or coronary spasm. The ostia of the coronaries are mainly affected and leads to life threatening complications. The Left Anterior Descending Artery is the main artery affected. The sequences in heart radiation may be rapid and end up in Acute Coronary Syndrome and Sudden Cardiac Death, but can stay progressive for many years post therapy. Women with malignancy in the left breast, the estimated mean dose of radiation to the heart applied is 6.6 GY, and tumor in the right breast is 2.9 GY, and with each 1.0 GY of radiation increase, there is 7.4% increase in the occurrence of subsequent major coronary event. This major event increases within 5 years of exposure to radiation and the risk continue up to 3 decades after Radiotherapy. The risk is greater at first 10 years after Cancer diagnosis. This means that a long surveillance protocol is needed to prevent the end stage of these dangerous side effects, which may terminate in a Sudden Cardiac Death and other various complications. To be noted here that there is no threshold level below which radiation therapy is safe to the heart and associated vascular system, and irradiation below 30 GY is regarded relatively as less damaging to the heart tissues.

Risk factors in these patients should be very well evaluated and properly managed to avoid any serious situations. We may face some residual risk of secondary effects due to the presence of normal tissues in the irradiation field remains. This can unfortunately affect the quality of life of breast cancer survivors, who are increasingly frequent. As a consequence, there is a need for further research to improve early detection of late cardiac effects in mostly asymptomatic patients, and also to improve prediction and prevention (Schultz-Hector 1998).

The BACCARAT project is a multidisciplinary novel approach to early detect radiation-induced cardiotoxicity based on an early stage clinical study. The long term significance of the observed changes being an important issue, at the end of the 2-year follow up of the study, each patient was proposed to participate in a large multicentric study on long term follow-up of cardiac events with clinical follow-up going foreword for 10 years at least (Schultz-Hector 1998) (Clarke2005).

Some hypothesis is investigated in BACCARAT (Clarke 2005), the choice of subclinical cardiac lesions index, the supervised analysis of targeted biomarkers, the methodology and clinical application for a precise heart dosimetry and doses constraints that could be enhanced during Radiotherapy, the choice to model and possibly predict the cardiotoxicity risk by combining biological, clinical and dosimetric parameters. Meta-

analysis, which allows the identification and abstraction of critical information from different randomized, controlled trials (Heit 2002) analyzed long term mortality from heart disease after Radiotherapy for an early breast cancer of about 300 000 women in United States Surveillance, Epidemiology and End Results (SEER) Cancer registries. It was found that for women diagnosed during 1973-82 and irradiated, the cardiac mortality ratio (left versus right tumor laterality) was 1.20 (95% CI 1.04-1.38) less than 10 years afterwards, 1.42 (1.11-1.82) 10-14 years afterwards, and 1.58 (1.29-1.95) after 15 years or more (trend: $2p = 0.03$), respectively (Roden DM 2004) For women diagnosed during 1983-92 and irradiated, the cardiac mortality ratio was 1.04 (0.91-1.18) less than 10 years afterwards and 1.27 (0.99-1.63) 10 or more years afterwards. For women diagnosed during 1993-2001 and irradiated, the cardiac mortality ratio was 0.96 (0.82-1.12). According to the interpretation of the results, since the early 1980s, improvements in Radiotherapy planning should have reduced mortality from heart disease in women received Radiotherapy.

Total body radiation can precipitate Tumor Lysis Syndrome caused by tremendous tumor disintegration and huge change in the body chemistry and accumulation of metabolites, leading eventually to Sudden Cardiac Death. We will talk in more details about this important subject of Tumor Lysis Syndrome as we go further.

ARRHYTHMIAS AND CARDIOTOXICITY

Arrhythmias are the main cause of Sudden Cardiac Death in the general pathologies, and with Cancer therapy, a wide range of arrhythmias formation were no exception to this rule, and tragedy is well observed in many situations leading to increased morbidity and mortality (ESC CPG position paper 2016).

We will try here to give more extensive talk about Arrhythmias, types and mechanism in association with Cardiotoxicity.

All physicians who are treating Cancer patients should expect the sudden induction of arrhythmias at any stage of management and should be prepared to treat effectively any Sudden Cardiac Death Events that may up rise, and according to The Guidelines Recommendations for the Management of Sudden Cardiac Deaths. We should be aware, as previously mentioned, that arrhythmias can be started by the Cancer itself or by the treatment of this Cancer. The patients usually have variable symptoms ranging from dizziness, palpitations, syncope, dyspnea, chest pain, neurological dysfunction and can end up with Transient Ischemic Attacks (TIAs), Stroke or Sudden Cardiac Death.

Arrhythmias are usually intermittent and Holter ECG monitoring for at least 24-72 hours is a must if symptoms appear, to capture these arrhythmias, their nature, duration, frequency and type. The arrhythmias can be in the form of Sinus Tachycardia, Brady Arrhythmias, Tachy Arrhythmias or Conduction Abnormalities (ESC CPG position paper 2016).

TYPES OF ARRHYTHMIAS IN CANCER TREATED PATIENTS

1. Primary:

Usually due to Ischemic Heart Disease, increased intra cardiac pressure, increased wall stress and Cardiomyopathies.

2. Secondary:

Usually due to cardiotoxicity of Cancer treatment.

It may also be due to increased sympathetic activity, electrolytes abnormalities and Radiotoxicity to the heart.

THE MAIN ARRHYTHMOGENIC CANCER DRUGS

1. Anthracyclines.
2. Arsenic trioxide.
3. 5 FU (5 Fluorouracil).
4. Irinotecan.
5. Gemcitabine.
6. Interferon.

USUAL TREATMENT OF SECONDARY ARRHYTHMIAS

1. Correction of body chemistry.
2. Removal of causative drug.
3. Strict and aggressive management of the arrhythmias according to the present Guidelines for the management of arrhythmias.

Table 1. List of Cancer drugs associated with cardiac arrhythmias
(ESC CPG position paper 2016)

Type of Arrhythmia	Causative drug
Bradycardia	Arsenic trioxide, bortezomib, capecitabine, cisplatin, cyclophosphamide, doxorubicin, Epirubicin, 5FU, ifosfamide, IL-2, methotrexate, Mitoxantrone, paclitaxel, rituximab, thalidomide.
sinus tachycardia	Anthracyclines, carmustine.
Atrioventricular block	Anthracyclines, arsenic trioxide, bortezomib, cyclophosphamide, 5FU, Mitoxantrone, rituximab, thalidomide.
Conduction disturbances	Anthracyclines, Cisplatin, 5FU, imatinib, taxanes
Atrial fibrillation	Alkylating agents (cisplatin, cyclophosphamide, melphalan), anthracyclines, antimetabolites (capecitabine, 5FU, gemcitabine), IL-2, interferons, rituximab, romidepsin, small molecule TKIs (ponatinib, sunitinib, ibrutinib), topoisomerase II inhibitors (amsacrine, etoposide), taxanes, vinca alkaloids.
Supra ventricular tachycardia	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide, melphalan), amsacrine, anthracyclines, antimetabolites (capecitabine, 5FU, methotrexate), bortezomib, Doxorubicin, IL-2, interferons, paclitaxel, ponatinib, romidepsin.
Ventricular tachycardia/fibrillation	Alkylating agents (cisplatin, cyclophosphamide, ifosfamide), amsacrine, antimetabolites (capecitabine, 5FU, gemcitabine), arsenic trioxide, doxorubicin interferons, IL-2, methotrexate, paclitaxel, proteasome inhibitors (bortezomib, carfilzomib), rituximab, romidepsin.
Sudden cardiac death SCD	Anthracyclines (reported as very rare), arsenic trioxide (secondary to torsade de pointes), 5FU (properly related to ischemia and coronary spasm), interferons, nilotinib, romidepsin.

5FU = 5 fluorouracil, IL-2 = interleukin 2, TKI = tyrosine kinase inhibitor.

Table from ESC CPG Position paper 2016.

SUPRA VENTRICULAR ARRHYTHMIAS (SV)

Frequently seen in Cancer patients. Most of the times there is difficulty in controlling these SV arrhythmias by drugs, in particular if they are of sustained type. Cardioversion usually will terminate these arrhythmias. Frequently in our clinical practice we are facing two important types of SV arrhythmias; Atrial Fibrillation (AF) and Atrial Flutter (AFI) and both should be treated in the same manner as in the non-Cancer patients. Pharmacological treatment should be given the priority before we intervene with Cardioversion.

Before Cardioversion we have to exclude the presence of thrombus in the Left Atrium especially the Left Atrial Appendage (LAA) by Transesophageal Echocardiography (TOE) or putting the patient on anticoagulation before the procedure of Cardioversion. This type of arrhythmias and in particular the Atrial Fibrillation are common post operatively, especially post lung resection surgery (ESC CPG position paper 2016). We will talk more about Atrial Fibrillation in the coming section due to its importance and frequency.

VENTRICULAR ARRHYTHMIAS

Can be initiated by Chemotherapy or Radiotherapy. The serious type of Ventricular Arrhythmias is the one created by the prolonged QT interval leading to the fatal outcome by the Torsade de Pointes (TdP) and induction of Ventricular Tachycardia and/or Fibrillation, the latter is a common cause of Sudden Cardiac Death. We will talk more about the role of the Long QT interval in Cancer treatment as we go foreword.

TUMOR LYSIS SYNDROME (TLS) AND CANCER THERAPY

This is an important life threatening condition that should be mentioned here for clinical practice point of view and to be very well recognized by the attending physicians.

Tumor Lysis Syndrome causes sever electrolytes imbalance that eventually end up by Arrhythmias and Sudden Cardiac Death (Mirrakhimov 2015).

ACUTE TLS

It is due to lysis and death of large sum of neoplastic tissue and could be precipitated by anti-Cancer treatment. The main cause of death in this condition is severe hyperkalemia and/or Renal Dysfunction.

Tumor Lysis Syndrome may occur in less than 72 hours after the start of chemotherapy for the treatment of leukemia and lymphoma. This is a rapid serious start of this complication that we should be aware of in the proper time.

Symptoms vary much and the following should be noticed by the attending physician and may give us a hint to the diagnosis of TLS:

Muscle weakness, fatigue, arthralgia, nausea and vomiting, dark cloudy urine, seizures and arrhythmias.

Blood tests may show hyperuricemia, azotemia, hyperphosphaturia, metabolic acidosis, hyperkalemia, hypocalcaemia. The latter two conditions may end up with arrhythmias and Sudden Cardiac Death.

Renal failure in TLS is caused by the precipitation of high uric acid and calcium phosphate in the renal tubules (Mirrakhimov 2015).

CHEMOTHERAPY DRUGS THAT MAY CAUSE TUMOR LYSIS SYNDROME (TLS)

1. 5 Fluorouracil (5FU).
2. Mitoxantrone.
3. 6 mercaptopurine.
4. Immunotherapy.
5. Steroids (even if given alone).

RADIOTHERAPY AND TLS: (MIRRAKHIMOV 2015)

As we mentioned in the Radiotherapy section above, Total body radiation can precipitate Tumor Lysis Syndrome, and is due to the tremendous tumor disintegration and huge change in the body chemistry leading to accumulation of different metabolites causing a very high levels of metabolites which are manifested in the form of hyperkalemia and hypercalcemia and other metabolites, that will initiate a Sudden Cardiac Arrest and Death.

MANAGEMENT OF TLS

Before starting the sessions of Chemotherapy or Radiotherapy we have to be sure that we have adequately rehydrated the patient and well controlled his serum electrolytes. If the condition has already started we need to put the patient under aggressive rehydration by Normal Saline. For the hyperuricemia, we can introduce Allopurinol 100-300 mg per day. Other medical management of renal failure including hemodialysis should be introduced if needed. Correction of electrolytes chemistry is an urgent critical management. Sudden Cardiac Arrest should be managed according to Guidelines recommendations.

PERICARDIAL TAMPONADE AND CANCER DRUGS

Pericardial Tamponade is a serious cardiac condition that can be caused by Cancer medications. This condition can lead to severe hemodynamic compromise and the development of Sudden Cardiac Death (Braunwald 1997).

Usually this occurs with anthracyclines treatment, but it can occur with cyclophosphamide, cytarabine and bleomycin. Usually there is typical chest pain, fever,

ST-T changes and large effusions that may lead to Tamponade. Echocardiography is the method of choice to diagnose Tamponade. Proper management of chest pain and the critical effusion are an urgent issues.

ACUTE HEMORRHAGE AND CANCER DRUGS

As we know very well, the Cancer existence itself will cause an abnormal coagulopathy state by different mechanisms. The Cancer medications may cause the same changes. Both acting together may lead to severe hemorrhage(s) and can end up into a Sudden Cardiac Death (ESC CPG position paper 2016) (24).

The acute massive bleeding in Cancer patients usually occurs in patients with head and neck tumors (Carotid Artery Rupture). But it can take place in Lung Cancers, Esophageal Cancer and Gastric Cancer (Retroperitoneal Hemorrhage).

The bleeding usually massive, difficult to control and needs proper intervention to save the life of the patient (Gagnon 1998).

Cyclophosphamide and Ifosfamide are the main chemotherapies that may cause a life threatening massive bleeding and usually it is in the form of a Hemorrhagic Cystitis. Broad spectrum Angiogenesis Inhibitors such as thalidomide can end up with a life threatening hemorrhages due to vascular disruption in the endothelium of blood vessels.

Radiation therapy when given with chemotherapy may induce massive bleeding also.

There is a reported cases of massive Vaginal Bleeding-Menorrhagia- during chemotherapy administration induced by severe Thrombocytopenia. The tumor itself can induce this bleeding by invasion of the surrounding tissues (Gagnon 1998).

PULMONARY-EMBOLISM (PE) AND CANCER DRUGS

One of the important causes of Sudden Cardiac Death is the development of the Pulmonary Embolism.

In Cancer patients, Pulmonary Embolism can be induced by the hypercoagulable Cancer state or due to the treatment of the Cancer by Chemotherapy, Radiotherapy or both.

Cancer patients have 2-3 fold liability for thrombosis than the non-Cancer patients and the prevalence is highest with metastatic lesions and/or established risk factors and usually the affected patients have poor prognosis.

Massive PE in Cancer patient is not infrequently under diagnosed. Pulmonary Embolism (PE) usually originates from Deep Vein Thrombosis in the lower limbs, pelvis and central venous catheters.

Chemotherapy can provoke the Blood Clotting Cascades which can start the Thrombo Embolic state.

The life threatening Arterial Thrombo Embolism was observed with the Angiogenesis Inhibitors such as thalidomide, also with anthracyclines and taxanes group. Venous Thrombo Embolism can affect 20% of hospitalized patients and has been associated with the treatment using the following anti-Cancer medications:

1. Alkylating agents
2. Angiogenesis inhibitors.
3. Histone deacetylase inhibitors.
4. Tyrosine kinase inhibitors TKI.
5. Cisplatin:

Cisplatin agent can trigger the aggregation of platelets, enhance thromboxane formation by platelets and activate the arachidonic acid pathways in platelets leading to thrombotic events such as Deep Vein Thrombosis and Pulmonary Embolism. The incidence of toxicity is around 18%.

6. Tamoxifen:

We should here mention this important commonly used Estrogen Selective Receptor Antagonist in Breast Cancer Management which is associated with increased thromboembolic events when used, and should be avoided in patients with previous history of thrombosis. Tamoxifen is used to prevent Breast Cancer in women and to treat Breast Cancer in men and women. It is a drug when taken in the presence of risk factors may lead to a Sudden Cardiac Death.

All patient should be put for risk factors stratification and any history of thrombosis, stroke or MI should be detailed and patients to be excluded from this treatment accordingly or delayed until the risk factors are well controlled.

7. Combination of chemotherapy with VEGF inhibitors:

Usually increases the risk and recurrence of Thrombo Embolism (Heit 2002), and VEGF inhibitors alone can induce type II toxicity and SCD through several mechanisms such as induction of prolonged QT interval, thrombosis formation, left ventricular dysfunction, hypertension induction or worsening the present one and stimulate the formation of Pulmonary Hypertension.

8. Bevacizumab:

Can precipitate Arterial Thrombo- Embolic events (ATEs) in the form of Myocardial Infarction, Ischemic Stroke, and Pulmonary Arterial Embolism in a rate of 3.8% and can end up by a life threatening Sudden Cardiac Death. ATEs can occur at any time during treatment, with median time of 3 months. Events are not related to dose or cumulative exposure. Bevacizumab should be discontinued if the ATEs occur during treatment.

9. Lenalidomide:

This is a Novel Targeted Therapy which has a significant risk for thrombosis and necessitating prophylactic treatment with either Aspirin or LMWH.

Cancer patients frequently undergo routine imaging studies that usually include chest CT scans. With the introduction of multidetector CT scanners, the detection of PE has become increasingly common, but reliable estimates on the prevalence, clinical characteristics and outcome of Cancer patients with PE are not well known. Its prevalence ranges from 1.0 to 6.0%, and both hospitalization at the time of CT scanning and the presence of cancer were associated with an increased prevalence. In real life, the majority of these patients are treated with anticoagulant therapy for at least 3 months, and their outcome in terms of recurrences, major bleeding or mortality seem not to differ from the outcome in non-cancer patients with symptomatic PE (Heit 2002) but the recommendation is to anti-coagulate the high risk patients who are hospitalized for surgeries and selected cases with multiple myeloma. It is not known whether Cancer patients have an altered risk of coronary thrombosis after stenting. However, the lack of randomized clinical trials and the limited number of observational studies do not allow firm treatment recommendations. New studies, involving more patients and a longer follow-up, are warranted.

QTC - INTERVAL PROLONGATION AND CANCER DRUGS

Special attention should be paid to the prolongation of the QT interval, using the corrected form of QTc interval, that may lead to sudden start of Torsade de Pointes (TdP) and commencement of the fatal Ventricular Fibrillation that can end up with the Sudden Cardiac Death (Roden DM 2004) (ESC CPG position paper 2016).

The QT interval should be controlled before, during and after treatment of Cancer patients. The risk of QT prolongation varies with different Cancer medications. The arsenic trioxide is the most relevant Cancer drug to be concentrated on, it prolongs the QT interval in 26-93% of patients and not infrequently leads to life threatening arrhythmias. The prolongation of the QT interval was observed 1-5 weeks after arsenic

trioxide infusion and returns to baseline at the end of 8 weeks. A 12 lead ECG should be recorded and the QT interval is to be corrected for heart rate with Bazett's or Fridericia's formula and should be obtained in all patients at baseline. Other causes for prolonged QT interval (correctable) should be identified and corrected properly (Table 3).

Safety and efficacy are the 2 paramount aspects of drug development. In general, the benefits of the pharmaceutical agent should outweigh any risk associated with it. In most instances, even a small risk of a serious complication cannot be tolerated (Goldberger 2006).

QTc monitoring is a central part of the drug approval process, and most pharmaceutical agents are subjected to the TQTS, a protocol established by the ICH to ensure appropriate QTc evaluation. Although it is well known that the QT interval is a poor surrogate for TdP, the potential for this life-threatening arrhythmia in the setting of a prolonged QTc has led to the withdrawal of several drugs from the market and more intense labelling and warnings for many others. This issue becomes more complex when dealing with Oncology pharmaceutical agents because the disease is often life threatening and alternative therapies may not exist (Grant 2009).

We have to be alert to risk factors that cause QT prolongation, the correctable and the non-correctable ones, so that we could manage the correctable factors and be able to deal with the non-correctable ones (Table 3).

Cancer drugs that may induce prolongation of QT interval (ESC CPG position paper 2016)
Doxorubicin, depsipeptide, vorinostat, axitinib, bosutinib, cabozantinib, dasatinib, crizotinib, lapatinib, nilotinib, pazopanib, ponatinib, sorafenib, sunitinib, vandetanib, vemurafenib, arsenic trioxide.
Table 2 ESC CPG position paper 2016

Table 3. Risk factors for QT Prolongation in Cancer Patients

Risk factors for QT prolongation	
Correctable	Non-Correctable
Electrolytes imbalance: * Nausea and emesis * Diarrhea * Treatment with loop diuretics * Hypokalemia (≤ 3.5 mEq/L) Hypomagnesaemia (≤ 1.6 mg/DL) * Hypocalcaemia (≤ 8.5 mg/dL)	<ul style="list-style-type: none"> • Family history of Sudden death (occult congenital LQTS or genetic polymorphisms). • Personal history of syncope • Baseline QTc interval prolongation • Female gender • Advanced age • Heart disease

Risk factors for QT prolongation	
Correctable	Non-Correctable
Hypothyroidism Concurrent use of QT prolonging drugs: * anti arrhythmic * anti infective * antibiotic * antifungal * Psychotropic * antidepressant * anti-psychotic * anti emetic * antihistamine	<ul style="list-style-type: none"> • MI • Impaired renal function • Impaired hepatic drug metabolism.
ESC CPG Position paper 2016	

Full 12 lead ECG must be available to detect the prolonged QT interval and not to depend only on the machine calculations. All calculations are preferred to be done manually by the attending physician and preferred to be using the Bazett's formula. Lead II and V5 are usually used for calculations.

CARDIOMYOPATHY AND CANCER MEDICATIONS

Cardiomyopathy is the traditional change in the heart due to Cancer drugs treatment by the Chemotherapy and Radiotherapy and obviously noticed in the form of a Left Ventricular Dysfunction (Table 4). These changes will progress into the stage of the commencement of the heart failure (this is described classically as Cardiotoxicity) and may end up with a Sudden Cardiac Death through different mechanisms. Pediatric Cancer survivors treated with anthracyclines and/or mediastinal Radiotherapy are at 15 fold increased life time risk for heart failure compared with controls.

Now we are much aware that treatment with tyrosine kinase inhibitors (TKIs) is increasing the incidence of LV dysfunction and Heart Failure, especially in the pre-existing risk factors in these patients (ESC CPG position paper 2016).

Table 4. Incidence of left ventricular dysfunction associated with chemotherapy drugs) (ESC CPG position paper 2016)

Chemotherapy agent	Incidence (%)
Anthracyclines	Dose dependent
Doxorubicin (Adriamycin)	
400 mg/m ²	3-5

Table 4. (Continued)

Chemotherapy agent	Incidence (%)
550 mg/m ²	7-26
700 mg/m ²	18-48
Idarubicin >90 mg/m ²	5-18
Epirubicin >900 mg/m ²	0.9-11.4
Mitoxantone >120 mg/m ²	2.6
Liposomal anthracycline	2
Alkylating agents	
Cyclophosphamide	7-28
Ifosfamide <10 g/m ²	0.5
12.5-16 g/m ²	17
Antimetabolites	
Clofarabine	27
Antimicrotubule agents	
Docetaxel	2.3-13
Paclitaxel	<1
Monoclonal antibodies	
Trastuzumab	1.7-20.1
Bevacizumab	1.6-4
Pertuzumab	0.7-1.2
Small molecule tyrosine kinase inhibitor	
Sunitinib	2.7-19
Pazopanib	7-11
Sorafenib	4-8
Dasatinib	2-4
Imatinib mesylate	0.2-2.7
Lapatinib	0.2-1.5
Nilotinib	1
Proteasome inhibitors	
Carfilzomib	11-25
Bortezomib	2-5
Miscellaneous	
Everolimus	<1
Temsirolimus	<1

Risk factors predisposing to Cardiotoxicity in general (ESC CPG position paper 2016):

1. Gender - female (> in females).
2. Age - 15< or >65 years
3. High BMI > 30 kg/m²

4. Previous LV dysfunction.
5. Presence of Hypertension.
6. Previous Radiotherapy, especially mediastinal.
7. Previous or pre-existing heart failure.
8. Significant Coronary heart disease.
9. Previous chemotherapy session.

The Cardiologist and/or the Oncologist must spend an enough time in history taking to obtain the presence or absence of the above risk factors. The treatment and further management will much depend on these factors. Files documentation system, electronic reporting, data collecting and exchange, should be optimum for all patients without exception, and to be the corner stone of all the workup activity in any Cardio-Oncology clinic.

CORONARY ARTERY DISEASE

Myocardial Ischemia and to a lesser degree, Myocardial Infarction inducing arrhythmias are side effects of several Cancer therapies and subsequently may end up with the tragedy of Sudden Cardiac Death if not properly managed (ESC CPG position paper 2016).

Find below in Table 5 the proposed mechanism of these ischemic changes and cancer drugs involved in initiation of these pathologies.

Table 5. Pathophysiological mechanisms of coronary artery disease in cancer treatment

Agent	Pathophysiological mechanism	Risk of CAD and ACS
Fluoropyrimidines	* Endothelial injury. * Vasospasm	* up to 18% manifest ischemia. * up to 7-10% silent myocardial ischemia.
Platinum compounds	* Procoagulant status. * Arterial Thrombosis	* 20 year absolute risk of up to 8% after testicular cancer * 2% risk of Arterial thrombosis.
VEGF inhibitors (bevacizumab, sorafenib, Sunitinib)	* Procoagulant status * Arterial Thrombosis * Endothelial injury	* Risk of Arterial Thrombosis.
Radiotherapy	* Endothelial injury * Plaque rupture * Thrombosis	* 2-7 fold increase relative risk of MI * Cumulative 30 year coronary events incidence of 10% in Hodgkin lymphoma survivors * Risk proportional to irradiation dose.

ATRIAL FIBRILLATION AND CANCER DRUGS AS A RISK FOR SUDDEN CARDIAC DEATH

We cannot end this important chapter dealing with the Sudden Cardiac Death associated with Cancer treatment without passing through the Atrial Fibrillation in more details. Atrial Fibrillation (AF) is the most common sustained arrhythmia being present in 1.5-2% of the population and has been found to occur more frequently in Oncology patients (ESC CPG position paper 2016) (Table 6). Among patients with history of Cancer, 18.3% had Atrial Fibrillation compared with 5.6% in people without. Cancer and Cancer therapy may seem to be risk factors for the development of AF and both share common risk factors, such aging. The occurrence of AF in Cancer may be due to comorbid states or a direct tumor effect, but it also may represent a complication of Cancer therapy, whereby inflammation is present for both conditions. The increasing survival of Cancer patients may further raise the incidence of the arrhythmia.

There are specific types of Cancer such as the pancreatic, ovarian, lung, and primary hepatic Cancers that may have an increased embolic risk. In addition, there are many Cancer therapies that also increase that risk of developing AF such as the cisplatin, gemcitabine, 5-fluorouracil, melphalan, docetaxel, etoposide, erythropoietin, granulocyte colony stimulating factors.

As mentioned above, Inflammation plays an important role in the process of Carcinogenesis and could provide a possible explanation for the relationship between Atrial Fibrillation, inflammation, and Cancer. CRP was found statistically elevated in patients with Atrial Fibrillation and Cancer (ESC CPG position paper 2016). This arrhythmic change of Atrial Fibrillation can precipitate the Sudden Cardiac Death. The management of AF in Cancer patients is similar to Non-Cancer individuals and should be applied properly and aggressively.

The role of Immune therapy in treating the inflammation induced Atrial Fibrillation is to be tested and the coming studies may clarify this possibility.

**Table 6. Epidemiological evidence of AF in patients with cancer
(ESC CPG position paper 2016)**

First author (year)	No. of patients
Hu et al. ³	24.125
Onaitis et al. (2010)	13.906
Wilkinson et al. (2010)	20.571

Source: Farmakis D, Parissis JA and Filippatos G., Insights into onco-cardiology: atrial fibrillation in cancer. *J. Am. Coll. Cardiol.* 2014; 63:945-53.

AF, atrial fibrillation.

CONCLUSION

The whole secret of successful Cardio-Oncology Medicine is the proper collaboration between Cardiologists, Oncologists, Hematologists, Nephrologists and the Primary Health Care Physicians to evaluate the Cancer patient before, during and after the therapy. All risk factors should be well controlled, all pathologies managed and all adverse effects of treatment to be overcome.

The issue of Sudden Cardiac Death is serious and fatal to the treated Cancer patients. We may lose the lucky survived Cancer patient by the same weapon applied to Cancer that is the Cancer medication.

All patients without exception should be well interrogated for their past and present medical history and thoroughly examined manually, using different equipment, referred to proper consultations and to put a good surveillance strategy to follow him/her in the short and long term.

All physicians attending with the Cancer patients should be aware of all the side effects of different therapies given and should be ready in a highly standard capability to manage these adverse effects that may appear on the surface at any time of the treatment.

Sudden Cardiac Death means that we are going to lose our valuable patient in a short period of time, so we have to be prepared to act faster than death, supported by our knowledge, training and faith.

REFERENCES

- Abdel-Qadir, H., J.L. Ethier, D.S. Lee, P. Thavendiranathan, and E. Amir. 2017. "Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis." *Cancer Treat. Rev.* 53:120-7.
- Bovelli, D., G. Plataniotis, and F. Roila. 2010. "Cardiotoxicity of chemotherapeutic agents and radiotherapy-related heart disease: ESMO Clinical Practice Guidelines." *Ann. Oncol.* 21(suppl. 5): v277-82.
- Braunwald, E. 1997. "Cardiac tamponade." In: *Heart disease: A textbook of cardiovascular medicine*, edited by E. Braunwald, 1446-96.
- Cardinale, D., A. Colombo, G. Bacchiani, I. Tedeschi, C.A. Meroni, M. Civelli, G. Lamantia, N. Colombo, C.M. Cipolla, F. Veglia, C. Fiorentini, and G. Curigliano. 2016. "Response to letters regarding article, early detection of anthracycline cardiotoxicity and improvement with heart failure therapy." *Circulation* 133(4):e363 doi: 10.1161/CIRCULATIONAHA.115.018780.
- Clarke, M., R. Collins, S. Darby, C. Davies, P. Elphinstone, V. Evans, J. Godwin, R. Gray, C. Hicks, S. James, E. MacKinnon, P. McGale, T. McHugh, R. Peto, C. Taylor,

- and Y. Wang. 2005. "Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials." *Lancet* 366(9503):2087-106.
- Davies, M.J. 1981. "Pathological view of sudden cardiac death." *Br. Heart J.* 45(1):88-96.
- Dhesi, S., M.P. Chu, G. Blevins, I. Paterson, L. Larratt, G.Y. Oudit, and D.H. Kim. 2013. "Cyclophosphamide-induced Cardiomyopathy: a case report, review and recommendation for management." *J. Investig. Med. High Impact Case Rep.* 1(1):2324 709613480346. doi: 10.1177/2324709613480346.
- Di Francia, R., A. De Monaco, M. Saggese, G. Iaccarino, S. Crisci, F. Frigeri, R. De Fillippi, M. Berretta, and A. Pinto. 2017. "Pharmacological profile and pharmacogenomics of anti-cancer drugs used for targeted therapy." *Curr. Cancer Drug Targets* doi: 10.2174/1568009617666170208162841.
- DiMaio, S.M., V.J. DiMaio, and J.B. Kirkpatrick. 1980. "Sudden, unexpected deaths due to primary intracranial neoplasms." *Am. J. Forensic Med. Pathol.* 1(1):29-45.
- Gagnon, B., I. Mancini, J. Pereira, and E. Bruera. 1998. "Palliative management of bleeding events in advanced cancer patients." *J. Palliat. Care* 14(4):50-4.
- Goldberger, A.L. 2006. *Clinical electrocardiography*. 7th edition. Philadelphia: C.V. Mosby Co.
- Grant, A.O. 2009. "Cardiac ion channels." *Circ. Arrhythm. Electrophysiol.* 2(2):185-94.
- Grenier, M.A., and S.E. Lipshultz. 1998. "Epidemiology of anthracycline cardiotoxicity in children and adults." *Seminars in oncology* 25(4 Suppl. 10):72-85.
- Harake, D., V.I. Franco, J.M. Henkel, T.L. Miller, and S.E. Lipshultz. 2012. "Cardiotoxicity in childhood cancer survivors: strategies for prevention and management." *Future Cardiol.* 8(4):647-70.
- Heit, J.A., W.M. O'Fallon, T.M. Petterson, C.M. Lohse, M.D. Silverstein, D.N. Mohr, and L.J. Melton. 3rd. 2002. "Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study." *Arch. Intern. Med.* 162(11):1245-8.
- Inagaki, J., V. Rodriguez, and G.P. Bodey. 1974. "Proceedings: causes of death in cancer patients." *Cancer* 33(2):568-73.
- Kufe, D.W., R.E. Pollock, R.R. Weichselbaum et al. 2003. *Cancer Medicine*, 6th edition. Hamilton (ON): BC Decker.
- Mirrahimov, Aibek E., Prakruthi Voore, Maliha Khan, and Alaa M. Ali. 2015. "Tumor lysis syndrome: a clinical review." *World J. Crit. Care Med.* 4(2):130-8.
- Moja, L., L. Tagliabue, S. Balduzzi, E. Parmelli, V. Pistotti, V. Guameri, and R. D'Amico. 2012. "Trastuzumab containing regimens for early breast cancer." *Cochrane Database Syst. Rev.* (4):CD006243. doi: 10.1002/14651858.CD006243.pub2.

- Priori, S.G., C. Blomström-Lundqvist, A. Mazzanti, N. Blom, M. Borggrefe, J. Camm, P.M. Elliott, D. Fitzsimons, R. Hatala, G. Hindricks, P. Kirchhof, K. Kjeldsen, K.H. Kuck, A. Hernandez-Madrid, N. Nikolaou, T.M. Norekvål, C. Spaulding, and D.J. Van Veldhuisen. 2015. "2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)." *Eur. Heart J.* 36(41):2793-867.
- Rabkin, S.W., and P. Sunga. 1987. "The effect of doxorubicine (adriamycin) on cytoplasmic microtubule system in cardiac cells." *J. Mol. Cell. Cardiol.* 19(11):1073-83.
- Roden, D.M. 2004. "Drug-Induced Prolongation of the QT Interval." *N. Engl. J. Med.* 350(10):1013-22.
- Schultz-Hector, S. 1992. "Radiation-induced heart disease: review of experimental data on dose response and pathogenesis." *Int. J. Radiat. Biol.* 61(2):149-60.
- Shoemaker, Laura K., Umesh Arora, and C.M. Rocha Lima. 2004. "5 Fluorouracil-induced coronary vasospasm." *Cancer control* 11(1):46-9.
- The American College of Obstetricians and Gynecologists. 2014. "Committee opinion no. 606: Options for prevention and management of heavy menstrual bleeding in adolescent patients undergoing cancer treatment." *Obstet. Gynecol.* 124(2 Pt 1):397-402.
- Volkova, M., and R. 3rd Russell. 2011. "Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment." *Curr. Cardiol. Rev.* 7(4): 214-20.
- Von Hoff, D.D., M.W. Layard, P. Basa, H.L. Jr Davis, A.L. Von Hoff, M. Rozencweig, and F.M. Muggia. 1979. "Risk factors for doxorubicin-induced congestive heart failure." *Ann. Intern. Med.* 91(5):710-7.
- Yeh, E.T., A.T. Tong, D.J. Lenihan, S.W. Yusuf, J. Swafford, C. Champion, J.B. Durand, H. Gibbs, A.A. Zafarmand, and M.S. Ewer. 2004. "Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management." *Circulation* 109(25):3122-31.
- Zamorano, J.L., P. Lancellotti, D. Rodriguez Muñoz, V. Aboyans, R. Asteggiano, M. Galderisi, G. Habib, D.J. Lenihan, G.Y. Lip, A.R. Lyon, T. Lopez Fernandez, D. Mohty, M.F. Piepoli, J. Tamargo, A. Torbicki, and T.M. Suter. 2016. "2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)." *European Heart Journal* 37(36):2768-801.

Chapter 11

THE ROLE OF NOVEL ECHOCARDIOGRAPHIC TECHNIQUES FOR PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

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ABSTRACT

Echocardiography constitutes the cornerstone for sudden cardiac death (SCD) risk stratification. Guidelines rely on the prognostic power of left ventricular ejection fraction (LVEF) to guide implantable cardioverter defibrillator (ICD) placement. However LVEF has important variability, and values obtained from different imaging modalities are not interchangeable. Furthermore novel echocardiographic techniques such as 3D echocardiography and strain imaging, are promising for improving patient selection. Mechanical dispersion (MD), a novel parameter derived from segmental strain analysis that reflects myocardial contraction heterogeneity, has shown to be particularly promising. The aim of this chapter is to review current evidence for ICD patient selection for primary prevention and discuss the role of upcoming technology in echocardiography and its potential impact for arrhythmic risk stratification.

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INTRODUCTION

Sudden Cardiac Death (SCD) remains an important health problem across the world (Fishman et al. 2010). Due to its unexpected nature, and the fact that it can be the first presentation among patients with different heart diseases, strategies to prevent SCD continue to be sought. During the past years the implantable cardioverter defibrillator (ICD) was introduced for both primary and secondary prevention of SCD. Its use is supported by multiple trials based on the common inclusion criteria of a depressed left ventricular ejection fraction (LVEF < 35). ICD trials selected this LVEF value as an entry criteria as they were designed to prove its usefulness to prevent cardiovascular mortality among high risk individuals rather than to identify optimal markers for risk stratification (Dagres and Hindricks 2013).

The latest ESC 2015 Guidelines recommend to implant an ICD in patients with symptomatic heart failure (NYHA Class II-III) and a LVEF ≤ 35 in patients on optimal medical therapy for at least 1 month, with a Class I indication, level of evidence A for ischemic (at least 60 days after a myocardial infarction) and B for non ischemic patients (Priori et al. 2015).

However the use of LVEF for risk stratification and patient selection for an ICD in the real world has been shown to be suboptimal. However a substantial number of patients who experience SCD may not have severely depressed LVEF. In the Maastricht Circulatory Arrest Registry an out of hospital arrest registry carried out in the Netherlands, among patients with echocardiographic data available who experienced a cardiac arrest only 49% had a LVEF < 40% (Gorgels et al. 2003). In the Oregon Sudden Unexpected Death Study 48% of patients who experienced SCD had a LVEF > 55% and only 30% of these patients had a LVEF < 35%. (Stecker et al. 2006). On the other hand in patients with reduced LVEF a substantial number of patients who receive an ICD, following current guidelines recommendations, will not benefit, as they will not experience arrhythmic events. This is exemplified by the SCD-HeFT trial in which the appropriate discharge rate was 5.1% per year (Bardy et al. 2005).

In a meta-analysis performed in post myocardial infarction patients, LVEF was found to have a sensitivity of 59% and a specificity of 78% for identifying patients with major arrhythmic events. (Bailey et al. 2001) Altogether this data suggests that LVEF is insufficient for SCD risk stratification, and other predictors are urgently needed.

NEW PREDICTORS FOR IMPROVING SCD RISK STRATIFICATION

Current trials that support the use of an ICD have included patients with LVEF < 40-35% using different imaging modalities despite the fact that LVEF among these are not

interchangeable. Even more most of the patients were recruited using on site measurements (lacking quality control) (Galderisi et al. 2011), and the precise method to calculate LVEF in some studies is not stated (Moss et al. 1996; Bardy et al. 2005; Moss et al. 2002).

Due to the important gap in patient risk stratification multiple parameters have been proposed to improve it. Arrhythmic events are caused by a complex interplay of factors in which an acquired or genetic vulnerability and transient precipitating factors (ischemia, electrolyte abnormalities, increased autonomic tone) combine, ultimately resulting in arrhythmic events. Therefore risk stratification tools have focused on identifying vulnerable conditions to better predict the risk of SCD.

Among some of the main approaches new modalities to identify scar, single photon emission computed tomography, positron emission tomography, and cardiac magnetic resonance (MRI) have shown to be promising (Dagres and Hindricks 2013). In particular cardiac MRI has shown to be useful to identify scar, and zones of heterogeneous scar with surviving islands of cells, which represent the most likely substrate for arrhythmic events. Using cardiac MRI with late gadolinium enhancement a scar involving >5% of the myocardium was found to be a risk factor for death or ICD discharge independent from LVEF (HR: 4.6, 95% CI: 1.8 to 11.8, p 0.002) (Klem et al. 2012). Nonetheless cardiac MRI is limited by its high cost and availability, which prevents its widespread clinical use for risk stratification of SCD.

NEW ECHOCARDIOGRAPHIC TECHNIQUES FOR SCD RISK STRATIFICATION

Without doubt echocardiography is the most highly available imaging modality for SCD risk stratification. Significant progress has been achieved over the traditional approach in which two-dimensional (2D) LVEF is applied for this purpose. Among the most notable developments three-dimensional echocardiography and myocardial strain imaging are worth noting and might inexpensively improve our current risk stratification process.

THREE-DIMENSIONAL EJECTION FRACTION

It is clear that patients with heart failure, will need to be tested and reassessed over time, as the values of LVEF are the entry criteria for most patients in whom an ICD is considered. Therefore it is important that changes in LVEF measured at different time

points reflect real changes in left ventricular function. This fact brings attention into the issue of test retest reproducibility, which can lead to spurious changes of LVEF over time.

Table 1. Variability and Test Retest reproducibility of 2D and 3D LVEF

Method	Inter-observer	Intra-observer	Test-Retest	Minimal change detected
2D Echo	0.040	0.033	0.047	11% change
3D Echo	0.027	0.017	0.022	6% change

Currently the most widely used method for this purpose is 2D echocardiography, in the last decade three-dimensional (3D) echocardiography has substantially evolved, and its availability increased worldwide, values derived from 3D have been incorporated by current guidelines and recommended as the technique of choice to measure volumes and LVEF. The use of 3D echocardiography to measure the LVEF, allows to measure the whole volume of the ventricle, avoiding geometric assumptions. Furthermore 3D LVEF has been shown to highly correlate with cardiac CMR, which is currently considered the reference method for LVEF assessment.

In clinical practice it is not uncommon to send a patient with previously borderline LVEF to a new echocardiographic exam to decide whether to implant an ICD. In patients with LVEF between 30-40%, 2D LVEF will be more prone to changes inherent to the technique. These will not reflect a real change in LVEF, as 2D methods have higher inter-observer and intra-observer variability and lower test retest reproducibility compared to 3D LVEF. Using 2D LVEF changes above 11% can confidently be attributed to a change in myocardial function, compared with 3D LVEF in which a 6% change can be detected (Thavendiranathan et al. 2013) Table 1.

However until now the role of 3D LVEF for improving risk stratification for SCD has not been studied. Therefore when the clinician needs to determine the candidacy for an ICD, current evidence is insufficient to recommend the use of 3D methods over conventional 2D. Studies looking at the potential benefit of using 3D LVEF for risk stratification for SCD are strongly needed.

Three-dimensional echocardiographic measurement of the LVEF, endocardial border is traced, completely surrounding the left ventricle for both end-diastolic and end-systolic frames. Latter automatic tracking is performed throughout the cardiac cycle, measuring the actual volume of the LV, avoiding geometric assumptions which are always present in 2D methods for assessing LVEF.

APPLYING STRAIN IMAGING TO IMPROVE RISK STRATIFICATION

Recently, strain which reflects the change of length or thickness of myocardial fibers, has been incorporated into routine clinical practice. Strain measured with speckle tracking echocardiography, is based on the presence of natural acoustic markers in ultrasound images, that work as a fingerprint for each myocardial segment. These markers can be followed over the cardiac cycle and allow to describe deformation of individual segments. During systole, the LV shortens (longitudinal and circumferential dimension) and twists along its long axis. Strain is a measure of myocardial deformation of a segment in relation to its original dimension and it is expressed as a percentage. Negative strain refers to a decrease in length (e.g., shortening - longitudinal and circumferential deformation) - and positive strain to the increase in length (e.g., thickening - radial deformation) compared to initial length. Complete description of this subject is contained elsewhere (Blessberger and Binder 2010). Global longitudinal strain (GLS) is measured by acquiring echocardiographic images from three apical views (four chamber, two chamber, three chamber view). From these views a region of interest (ROI) that encloses the myocardium is selected, and strain can be calculated. Strain has quickly become an useful measurement that improves the evaluation of myocardial function. Studies looking at reference values have been conducted, in which GLS lower limit of normality has been established in -18% (Kocabay et al. 2014; Lang et al. 2016). In the following sections the role of strain imaging in specific diseases for SCD risk stratification will be reviewed.

ISCHEMIC HEART DISEASE

Patients with ischemic heart disease constitute the highest burden of patients who experience SCD, and the highest number of patients that have been included in ICD trials. Therefore evidence supporting the role of an ICD for primary prevention is substantially more robust in this patient subset. It is clear as previously stated that the current approach that relies mainly in LVEF, although useful is insufficient. The role of novel risk markers to improve patient selection is promising.

When evaluating the risk of SCD after a myocardial infarction, time from its occurrence becomes very relevant, as data suggests that the highest risk of SCD occurs early after a MI. In the VALIANT study which included over 14,000 patients with LV dysfunction after an acute MI, SCD occurred in 1.4% in the first month compared to 0.14% per month after two years. Risk was substantially higher in patients with a LVEF < 30% in whom the event rate was 2.3% for the first month. Therefore it would seem that the early period after a MI is the optimal period in which and ICD could be beneficial.

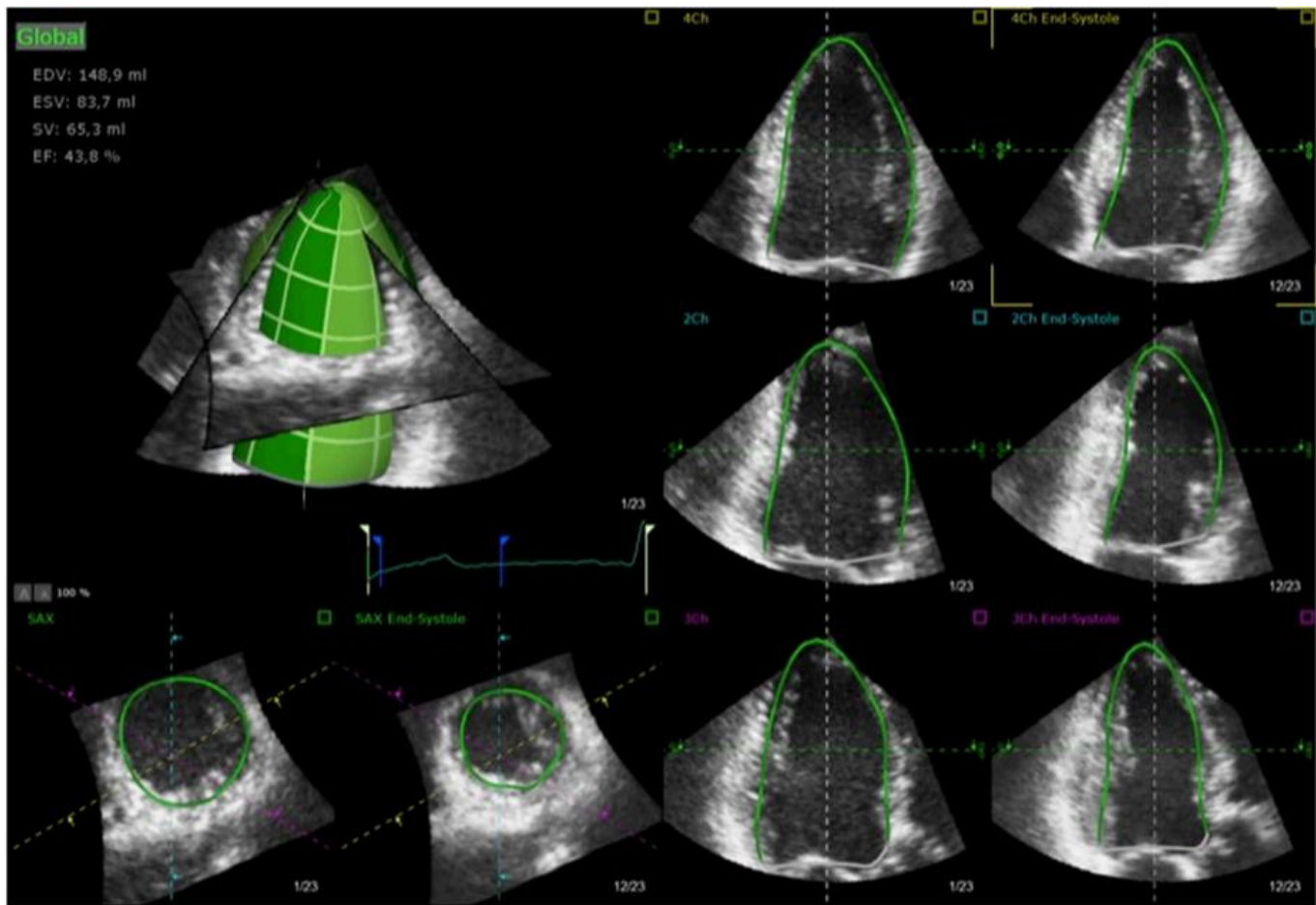


Figure 1. Three-Dimensional LVEF measured with semi-automatic vendor specific software.

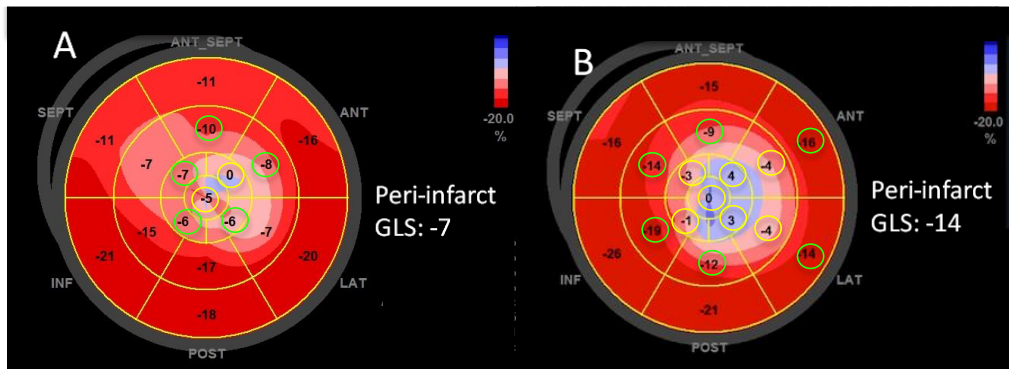


Figure 2. Peri-infarct zone strain analysis.

However risk stratification in the first months after STEMI is complicated and current guidelines do not recommend an in this period, as studies have failed to show benefit.

From a pathophysiological point of view the arrhythmic substrate evolves as stunned myocardium improves its function, and fibrosis ensues in the necrotic regions. Data from MADIT II shows that patients implanted with an ICD in whom a MI occurred more than 18 months before recruitment had the most significant survival benefit. This fact supports the concept that arrhythmogenic substrate might evolve after an acute MI.

Among patients with ischemic cardiomyopathy, GLS has been shown to be related to increased risk of ventricular arrhythmias after an ST elevation MI (HR 1.1 to 1.4 95% CI, $p = 0.004$) (Ersbøll et al. 2013). As GLS has been related previously with the size of the infarction, it is likely that lower GLS values reflect a larger infarction. Particularly important is the concept of the existence of zones of heterogeneous scar with surviving islands of cells, which may act as the substrate of arrhythmic events introduced by CMR. STE can also be used for this purpose and evidence has been published regarding the role of strain analysis in the border zone of MI. Each 1% drop in strain in this area was found to be independently associated with ventricular arrhythmias (HR 1.22; 95% CI 1.09-1.36; $p < 0.001$), and a peri-infarct strain $<9.9\%$ has shown to identify a higher risk group for arrhythmic events among patients with chronic ischemic heart disease (Ng et al. 2010) Figure 2.

Panel A shows a patient with chronic ischemic heart disease and previous distal LAD territory STEMI. The infarct zone is defined as segments with an absolute value below -5%. Peri-infarct zone strain is low, this patient experienced ventricular tachycardia during follow up after 12 months. Panel B shows a patient with a previous STEMI mid LAD, free of arrhythmic events after 48 months follow-up, note peri-infarction strain is relatively preserved.

As GLS analysis provides information regarding shortening of individual segments, time to maximal shortening can be measured in all segments of the LV. By measuring standard deviation of 16 segments mechanical dispersion (MD) can be obtained. This novel parameter is a measure of heterogeneity of myocardial contraction that has gained

interest not only to assess dyssynchrony but also to reflect susceptibility of the myocardium to ventricular arrhythmia (Figure 3).

Strain curves from two different apical views (Panels A and B), GLS with a value of -13.3, with the corresponding Bull's eye showing decreased strain in the basal inferior and inferolateral segments. Mechanical dispersion is calculated by measuring the time from the peak of the R wave to maximum shortening of each segment, and calculating the SD for all segments (White arrows, panel B). Calculation yielded a MD of 54 ms.

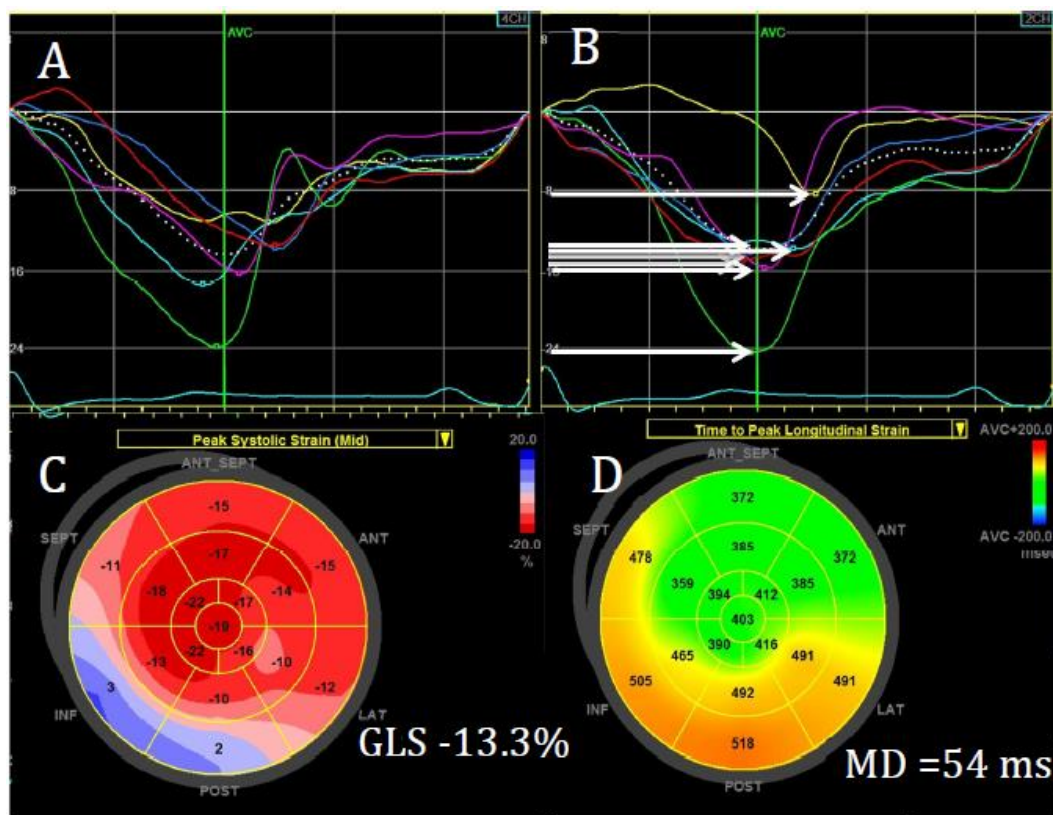


Figure 3. Global longitudinal strain and Mechanical Dispersion derived from 2D GLS.

MD has been shown to be useful to improve conventional risk stratification in patients with STEMI and NSTEMI after 40 days, early after a STEMI and in patients with chronic ischemic heart disease. In a groundbreaking prospective multicenter study (Kristina H. Haugaa et al. 2013) that recruited 569 patients with STEMI and NSTEMI > 40 days after the event, MD was found to be an independent predictor of ventricular arrhythmias, with a HR of 1.7 (95% CI 1.2-2.5; $p < 0.001$) for each 10 ms. increase. Importantly from this study is the fact that among patients with LVEF > 35% MD was consistently shown to be a predictor of arrhythmic events emerging as a tool that could be useful to identify patients at risk who do not fulfill current guideline recommendations. Although the study was not designed to establish the optimal cut-off, this group found

MD above 75 ms. as a useful measure to predict increased risk of cardiac arrhythmia among patients with previous myocardial infarction. Figure 3.

Speckle tracking echocardiography showing GLS and MD in two patients with NSTEMI > 40 days. A patient with mildly reduced EF and reduced strain with MD within normal limits, (Panel A and B) this patient did not have arrhythmic episodes after 48 months follow up. Another patient with a NSTEMI with similar EF, normal strain values and increased MD, this patient was admitted for a cardiac arrest after 24 months follow up.

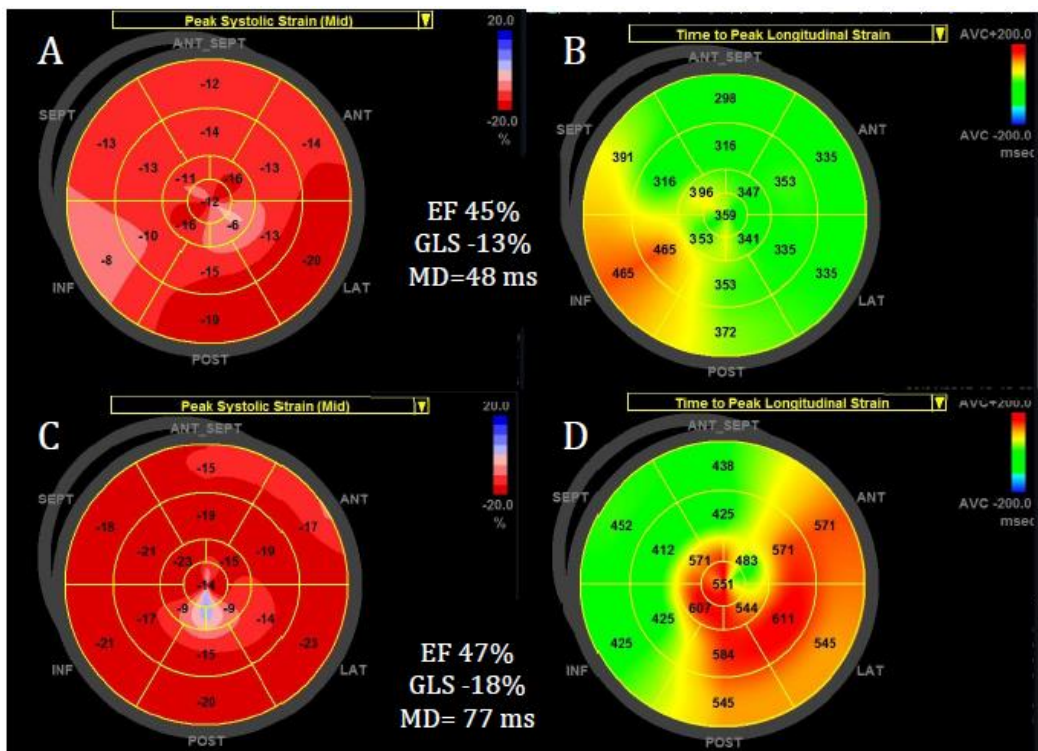


Figure 3. Strain analysis for risk stratification in patients with a previous myocardial infarction.

DILATED CARDIOMYOPATHY

Patients with non-ischemic dilated cardiomyopathy (DCM) also represent a substantial population prone to SCD. Patients with DCM do not constitute an homogeneous population. DCM more commonly affects men, and genetic defects, myocarditis, drugs or toxins may be responsible the LV dysfunction and myocardial changes that occur in these patients.

In patients with DCM substantially less evidence supports the use of an ICD for primary prevention among this patient subset. This fact is reflected by recommendations

from current guidelines that give a lower level of evidence for patients with dilated cardiomyopathy (IB). Recommendations are based on results from the COMPANION trial, which is the sole trial which demonstrated reduced all cause mortality and SCD by using chronic resynchronization therapy defibrillator (CRTD) and pooled analysis from other three trials. Recently the DANISH trial has failed to show a difference in all cause mortality with the use of an ICD in patients with DCM (HR = 0.87, CI 95% 0.68-1.12, $p = 0.28$), however it found a lower risk of SCD in patients implanted with an ICD (HR 0.5, 95% CI 0.31-0.82, $p = 0.005$). These negative results highlight the fact that by including patients using LVEF, not only patients who are at risk of SCD are implanted with an ICD, but also patients with a higher risk of death from causes not preventable by an ICD. It is thus of outmost importance to identify risk markers with higher specificity for arrhythmia in patients with DCM to identify patients in whom arrhythmic events would account for the increased risk of all cause mortality.

In patients with DCM, global longitudinal strain has been shown to be an important predictor of prognosis, and to be better to discriminate patients free of events than LVEF alone (Mignot et al. 2010). LVEF had an AUC of 0.73 and sensitivity of 73% and specificity of 58% with 29.5% as a cut-off, while GLS performed substantially better with -7% as the cut-off (AUC = 0.83, sensitivity 73% specificity 83%) (Mignot et al. 2010).

The role of strain imaging for improving arrhythmic risk stratification for SCD has been addressed only by one study. Among patients with DCM both GLS (HR = 1.26 95%CI 1.03-1.54, $p = 0.02$, per 1% increase) and MD (HR = 1.20 95%CI 1.03-1.40, $p = 0.02$, per 10 ms. increase) were found to be risk markers of all cause mortality and arrhythmic death, while LVEF was not independently associated (Kristina H. Haugaa et al. 2012). Among these patients MD > 72 ms. was shown to be related to higher event rate over a median follow up of 22 months (long rank $p < 0.01$).

MD is in concept a measure of dyssynchrony, although studies looking at dyssynchrony assessment with imaging methods have not consistently shown advantages over electrical dyssynchrony criteria using QRS duration, for identifying responders, they support the fact that dyssynchrony is an important determinant of arrhythmic risk. Among patients with DCM in whom CRT was implanted and MD measured before and 6 months after implantation, patients who experienced arrhythmic events had more pronounced MD at 6 months (112 ± 47 vs. 80 ± 30 ms., $P < 0.001$) and MD was found to be an independent predictor of arrhythmic events (HR 1.20, 95% CI 1.06-1.35, $p = 0.005$, for each 10 ms. increase). Among patients who did not experienced events, MD decreased at 6 months, supporting the concept that CRT might decreases the arrhythmic risk by decreasing dyssynchrony (Hasselberg et al. 2016).

Although clearly more research is needed to systematically apply MD as a risk marker to guide ICD implantation in patients with DCM, patients with higher MD seem to be at significant higher risk of experiencing SCD. Until more evidence is available it

seems reasonable to use clinical judgment, to evaluate patient's individual risk to decide whether to implant an ICD in patients who do not fulfill current guideline recommended criteria.

OTHER CARDIOMYOPATHIES

Long QT Syndrome

Long QT syndrome (LQTS), constitutes a pure electrical model, in which risk stratification of SCD can be studied without the complex confounding factors that exist in other diseases. In patients with LQTS ion channels are altered, causing increased cardiac action potential duration, consequently leading to an increased risk of ventricular arrhythmias and SCD. Patients with LQTS have electrical disturbances, which in turn may generate mechanical disturbances and result in prolonged contraction duration. By measuring MD the degree of electrical dispersion can be non-invasively assessed by using strain imaging, and this applied to identify patients at risk of arrhythmic events among carriers with LQTS.

LQTS was the first disease model in which MD was first demonstrated to be useful for arrhythmic risk assessment. In patients with symptomatic LQTS higher values of MD were found compared to asymptomatic carriers of LQTS (45 ± 13 ms. vs. 27 ± 12 ms, $p < 0.001$). Furthermore MD was found to have a higher area under the curve for arrhythmic events (AUC 0.87, 95% CI, 0.79 to 0.94) than corrected QT interval, the most widely used parameter for risk stratification among these patients, for the same purpose (0.71; 95% CI, 0.61 to 0.81; $P 0.01$). This suggests MD can importantly add to the conventional risk assessment of these patients, as many patients that have been identified to be mutation carriers do not develop events (Kristina Hermann Haugaa et al. 2010). Recent research has also shown that among patients with LQTS different genetic traits might also impact left ventricular mechanics in different degrees with higher compromise among patients with type 2 LQTS.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most frequent genetic heart disease worldwide. It is most commonly an autosomal dominant disease, in which the sarcomeric proteins genes are affected, however in 25-30% of the cases etiology is still unknown. Diagnostic criteria include a LV wall thickness >15 mm in one or more LV myocardial segments in the absence of an alternate disease that explains hypertrophy. Because SCD

affects patients with HCM at younger ages, estimation of SCD risk is an integral part of clinical management. Several features reflect an increased risk of SCD among adults with HCM. Previous guidelines recommended to use the presence of non-sustained ventricular tachycardia, maximal wall thickness ≥ 30 mm, family history of SCD, unexplained syncope and abnormal blood pressure response to exercise to guide ICD therapy. However the discriminative power of these features is only modest, and no randomized trial or prospective predictive model existed until recently. The 2014 ESC guidelines on diagnosis and management of patients with hypertrophic cardiomyopathy proposed an algorithm that was prospectively validated and is now key to decide to implant an ICD.

Electrophysiological studies have shown that patients with malignant arrhythmias have dispersed electrical activation probably due to interplay of myocardial disarray, micro vascular dysfunction, ischemia and sympathetic alterations. Ultimately resulting in ventricular arrhythmias and SCD.

New imaging modalities that can further contribute to refine risk assessment. LGE measured by cardiac MRI has been shown to be associated with increased risk of SCD, (HR 1.46, 95% CI 1.12-1.92, $p = 0.002$ for each 10% of LGE) (Chan et al. 2014). However evidence is insufficient to include LGE as a criteria to guide ICD implantation, and has not been yet included in guidelines. In a meta analysis which included 3067 patients the extent of LGE did not demonstrated to be independently associated with SCD after meta regression analysis ($p = 0.35$) (Briasoulis et al. 2015). This fact can be explained by the inability of conventional MRI sequences to detect interstitial fibrosis which seems to be more closely related to arrhythmic risk (Almaas et al. 2014).

The role of strain imaging for risk stratification in patients with HCM seems particularly promising. In a study in 92 patients with HCM who underwent ICD implantation, GLS was independently associated with the occurrence of appropriate ICD therapy (HR 1.15, 95% CI 1.12-1.3, $p = 0.03$). Using a GLS absolute value of 14% a significant difference of survival free of ICD therapy was clearly shown (log rank, $p = 0.003$). Even more MD has shown to be useful to improve arrhythmic risk stratification among patients with HCM. In a study of 150 patients with HCM, patients who developed ventricular arrhythmias had lower strain values ($-14.1 \pm 3.6\%$ vs. $-16.3 \pm 3.4\%$, $p < 0.01$), more qualitatively assessed presence of LGE (50% vs. 90%, $p = 0.03$), and higher MD (79 ± 27 ms. Vs. 59 ± 16 ms. $P < 0.001$). After multivariate analysis only age and MD were found to be independently associated with an increased risk of ventricular arrhythmias (HR 1.57 CI 95% 1.09-2.28, per 10 ms. increase). A significant arrhythmia free outcome was found in Kaplan Meier analysis in patients with MD < 67 ms., suggesting patients with higher values are at increased risk for this outcome. Furthermore by incorporating MD into current clinical risk algorithms including the recommended by the ESC guidelines, risk stratification was significantly improved (Haland et al. 2016).

Strain analysis in a patient with HCM with appropriate ICD therapy. Segmental peak systolic strain and MD were measured from four-chamber, (A) two-chamber, (B) and three-chamber view (C). Decreased GLS and prolonged MD were found.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic cardiomyopathy (ARC) is an inherited autosomal dominant disease that predominantly affects the right ventricle. In patients with ARC fibro fatty replacement of the myocardium occurs, leading to increased risk of arrhythmia, SCD and rarely heart failure. Its diagnosis requires a combination of clinical, ECG, Holter monitoring, genetic and imaging criteria which have been addressed by a Task Force on this subject in 2010 (Marcus et al. 2010). SCD can occur in early phase ARC, in which anatomic changes are subtle, and be the initial clinical presentation in up to 50% of patients. Strain echocardiography is particularly important as both right ventricular free wall strain (RV FWS), and RV GLS have been shown to be reduced early in the natural history of the disease. The concept of MD has also been explored in this patient subset, RV MD is measured from a RV focused view with adequate visualization of the RV free wall. From this view subsequent tracing of the RV endocardium is performed. The measurement of time to peak strain of the six segments studied from this view derives the value of RV MD. Figure 5.

RV strain measurement in a patient with ARC, a region of interest that includes the RV free wall and the interventricular septum are traced from the RV focus chamber view (A). Strain curves are displayed, from these either RV FWS or RV GLS are calculated, the latter is always lower as it includes strain values from the septum (B). Time to peak strain for each segment is shown, from these values RV MD is calculated as the standard deviation of six segments (C).

In patients in early stage ARC, it is important to differentiate this entity from right ventricular outflow tachycardia (RVOT) as this has a relatively innocent prognosis compared to ARC in which patients can present with SCD. The use of RV FWS is not helpful to achieve this differential, however RV MD has been found to be indeed higher in patients with early ARC compared to RVOT (22 ± 15 ms. vs. 15 ± 11 ms., $p = 0.03$). Decreased RV FWS is independently associated with the possibility of having early ARC compared (OR = 1.09, CI 95% 1-1.18, $p = 0.04$,) (Saberniak et al. 2016).

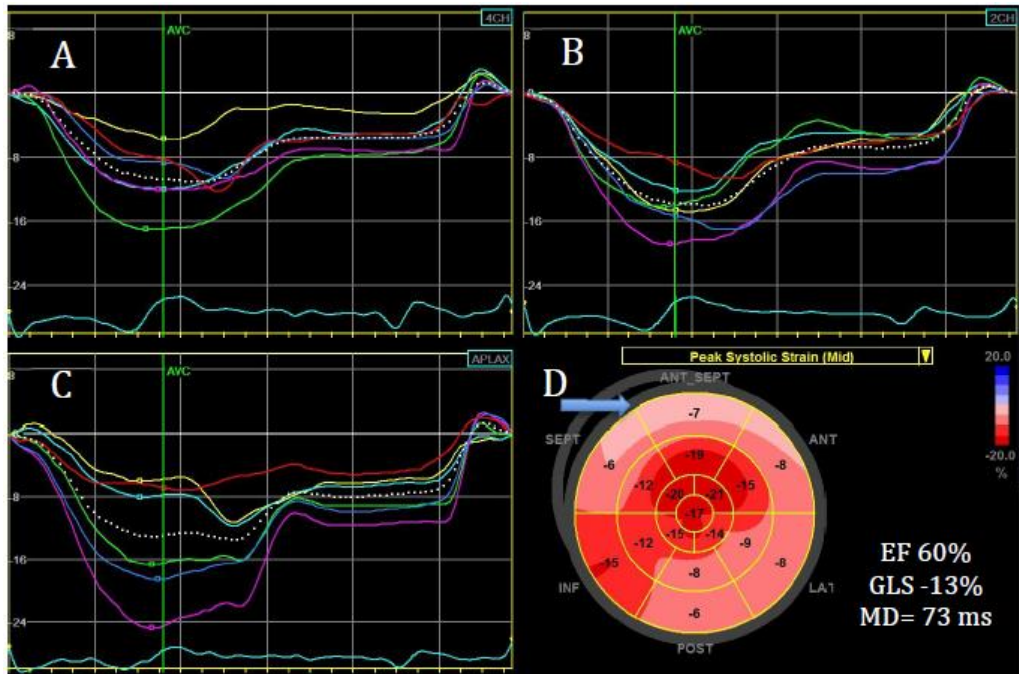


Figure 4. Global Longitudinal Strain and Mechanical Dispersion in a patient with HCM.

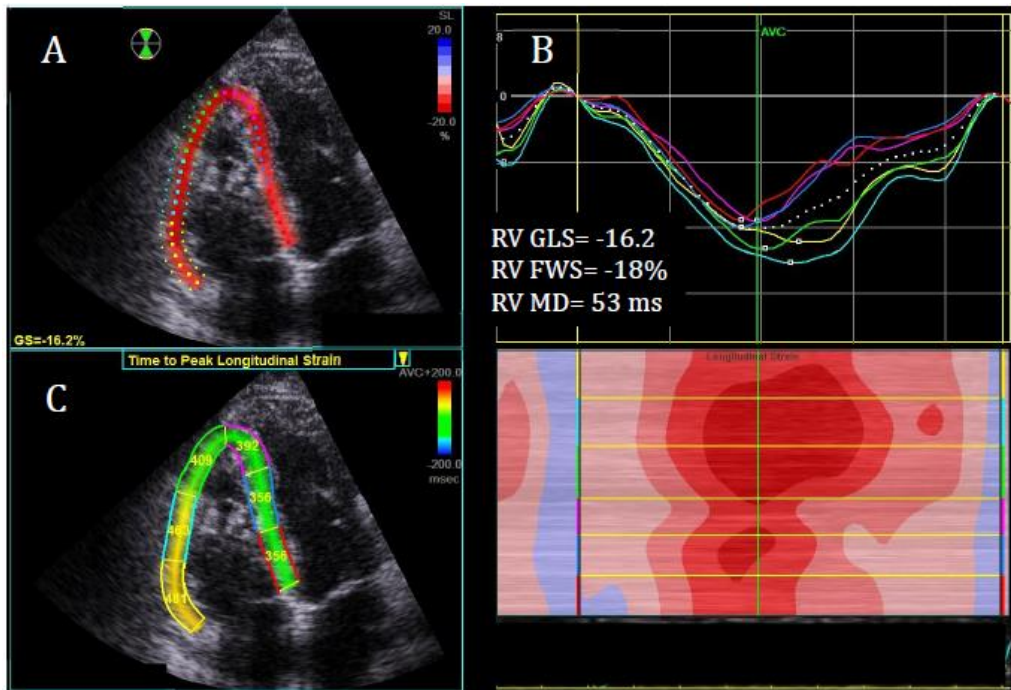


Figure 5. RV strain and MD measurement.

In patients with ARVC mechanical dispersion differs from normal patients, and seems interesting as a tool to improve risk stratification. In a study performed in

asymptomatic carriers and symptomatic patients with ARC both RV and LV MD were prolonged compared to healthy controls suggesting the presence of subclinical myocardial alterations. RV MD was identified as an independent predictor of arrhythmia in the multivariate analysis (OR 1.71, 95% CI 1.04-2.58, $p = 0.03$, per 10 ms. increase) (Sarvari et al. 2011). Although evidence is still emerging, it seems likely that strain imaging might have an important role in the near future both for diagnosis and prognostic stratification for SCD in patients with ARC. Very recently its role has been highlighted in an expert consensus document of the European Association of Cardiovascular Imaging (Kristina H. Haugaa et al. 2017).

Chagas Cardiomyopathy

Although Chagas cardiomyopathy (CC) is not a common cause of SCD worldwide, it affects more than 8 million patients, and most will develop the chronic form of the disease in which SCD accounts for substantial mortality. Importantly the use of an ICD in patients with CC has shown to an impressive reduction of all cause mortality (HR 0.28, 95% CI 0.11-0.72, $p = 0.007$) and SCD (HR 0.05, 95% CI 0.01-0.045, $p = 0.006$), supporting the notion that CC is a disease model with highly prevalent arrhythmic events. In patients with CC, MD and GLS have been found to be independently associated with previous history of arrhythmic events and ICD implanted in secondary prevention in patients with CC who were divided according to ICD status. (Barros et al. 2016) Evidence for primary prevention with ICD implantation in patients with CC is lacking and thus the role of novel parameters for risk stratification such as MD seem particularly important. In the meantime recent ESC guidelines are available and recommend implanting an ICD in patients with CC and an EF <40%, as all cause mortality has not been found to be reduced in patients with an EF > 40% who undergo ICD implantation (Priori et al. 2015).

LIMITATIONS OF SPECKLE TRACKING ECHOCARDIOGRAPHY

Although STE has significantly contributed to improve the evaluation of LV function and has the potential to improve SCD risk stratification, certain limitations of the technique should be stated. First, strain has been considered a less load dependent measure, however variations in loading conditions can lead to different results. This fact becomes important in patients with acutely decompensated heart failure in which therapy and improvement in loading conditions might lead to different values. Second as calculations for strain-derived parameters are derived from 2D images the presence of artifacts (shadowing, reverberations) can lead to inadequate tracking and inaccurate strain and MD values. This is especially true when several segments are not correctly tracked.

Third, strain values among vendors are not interchangeable. The impact of this issue regarding mechanical dispersion has not been specifically addressed however as tracking algorithms differ among vendors MD might be very likely also affected by inter-vendor variability. Lastly the adequate measurement of strain needs training and results from less experienced operators differ from more experienced ones.

IMPLEMENTING STRAIN AND MECHANICAL DISPERSION INTO CLINICAL PRACTICE

When implementing a new parameter such as MD in clinical practice, the availability, training requirements and time taken for analysis become relevant for the clinician. As strain is computed from standard echocardiographic views, and most commercially available machines now include the possibility to measure strain, it has the potential to become a widely used technique for improving risk assessment. However its measurement does require training to produce reproducible and accurate results. Adding the calculation of strain and MD for a patient is not a time consuming task, and adds in average 5 minutes to the standard echocardiographic exam.

CONCLUSION

The use of LVEF continues to be an important determinant of risk of arrhythmic events among patients with ischemic and non-ischemic cardiomyopathy. However a substantial number of events occur among patients with LVEF > 35%, who are not candidates for ICD implantation according to current guidelines. Novel echocardiographic techniques offer the possibility to refine the assessment of LV function, and provide a useful tool to identify patients at risk of SCD, specially among patients who do not fulfill guideline criteria. Both GLS and MD are promising tools, and their role is expanding to other diseases in which SCD risk stratification still needs to be improved. However further research confirming their role is needed to allow for these to be implemented in current clinical practice.

REFERENCES

Almaas, Vibeke M, Kristina H Haugaa, Erik H Strøm, Helge Scott, Hans-Jørgen Smith, Christen P Dahl, Odd R Geiran et al. 2014. "Noninvasive Assessment of Myocardial

- Fibrosis in Patients with Obstructive Hypertrophic Cardiomyopathy.” *Heart (British Cardiac Society)* 100 (8): 631-38. doi:10.1136/heartjnl-2013-304923.
- Bailey, James J., Alan S. Berson, Harry Handelsman, and Morrison Hodges. 2001. “Utility of Current Risk Stratification Tests for Predicting Major Arrhythmic Events after Myocardial Infarction.” *Journal of the American College of Cardiology* 38 (7). Elsevier Masson SAS: 1902-11. doi:10.1016/S0735-1097(01)01667-9.
- Bardy, Gust H., Kerry L. Lee, Daniel B. Mark, Jeanne E. Poole, Douglas L. Packer, Robin Boineau, Michael Domanski et al. 2005. “Amiodarone or an Implantable Cardioverter Defibrillator for Congestive Heart Failure.” *New England Journal of Medicine* 352 (3): 225-37. doi:10.1056/NEJMoa043399.
- Barros, Marcio V L, Ida S. Leren, Thor Edvardsen, Kristina H. Haugaa, Andre A L Carmo, Thais A R Lage, Maria Carmo P Nunes, Manoel O C Rocha, and Antonio L P Ribeiro. 2016. “Mechanical Dispersion Assessed by Strain Echocardiography Is Associated with Malignant Arrhythmias in Chagas Cardiomyopathy.” *Journal of the American Society of Echocardiography* 29 (4). Elsevier Inc: 368-74. doi:10.1016/j.echo.2015.12.008.
- Blessberger, Hermann, and Thomas Binder. 2010. “Two Dimensional Speckle Tracking Echocardiography: Clinical Applications.” *Heart* 96 (24): 2032-40. doi:10.1136/hrt.2010.199885.
- Briasoulis, Alexandros, Sagar Mallikethi-Reddy, Mohan Palla, Issa Alesh, and Luis Afonso. 2015. “Myocardial Fibrosis on Cardiac Magnetic Resonance and Cardiac Outcomes in Hypertrophic Cardiomyopathy: A Meta-Analysis.” *Heart (British Cardiac Society)* 101 (17): 1406-11. doi:10.1136/heartjnl-2015-307682.
- Chan, Raymond H, Barry J. Maron, Iacopo Olivotto, Michael J Pencina, Gabriele Egidio Assenza, Tammy Haas, John R Lesser et al. 2014. “Prognostic Value of Quantitative Contrast-Enhanced Cardiovascular Magnetic Resonance for the Evaluation of Sudden Death Risk in Patients with Hypertrophic Cardiomyopathy.” *Circulation* 130 (6): 484-95. doi:10.1161/CIRCULATIONAHA.113.007094.
- Dagres, Nikolaos, and Gerhard Hindricks. 2013. “Risk Stratification after Myocardial Infarction: Is Left Ventricular Ejection Fraction Enough to Prevent Sudden Cardiac Death?” *European Heart Journal* 34 (26): 1964-71. doi:10.1093/eurheartj/ehf109.
- Ersbøll, Mads, Nana Valeur, Mads Jønsson Andersen, Ulrik M. Mogensen, Michael Vinther, Jesper Hastrup Svendsen, Jacob Eifer Møller et al. 2013. “Early Echocardiographic Deformation Analysis for the Prediction of Sudden Cardiac Death and Life-Threatening Arrhythmias after Myocardial Infarction.” *JACC: Cardiovascular Imaging* 6 (8): 851-60. doi:10.1016/j.jcmg.2013.05.009.
- Fishman, G. I., S. S. Chugh, J. P. DiMarco, C. M. Albert, M. E. Anderson, R. O. Bonow, A. E. Buxton et al. 2010. “Sudden Cardiac Death Prediction and Prevention: Report From a National Heart, Lung, and Blood Institute and Heart Rhythm Society

- Workshop.” *Circulation* 122 (22): 2335-48. doi:10.1161/CIRCULATIONAHA.110.976092.
- Galderisi, Maurizio, Michael Y. Henein, Jan Dhooge, Rosa Sicari, Luigi P. Badano, José Luis Zamorano, and Jos R T C Roelandt. 2011. “Recommendations of the European Association of Echocardiography How to Use Echo-Doppler in Clinical Trials: Different Modalities for Different Purposes.” *European Journal of Echocardiography* 12 (5): 339-53. doi:10.1093/ejechocard/jer051.
- Gorgels, Anton P M, Claudia Gijbbers, Jacqueline De Vreede-Swagemakers, Aimee Lousberg, and Hein J J Wellens. 2003. “Out-of-Hospital Cardiac Arrest - The Relevance of Heart Failure. The Maastricht Circulatory Arrest Registry.” *European Heart Journal* 24 (13): 1204-9. doi:10.1016/S0195-668X(03)00191-X.
- Haland, Trine F., Vibeke M. Almaas, Nina E. Hasselberg, Jørg Saberniak, Ida S. Leren, Einar Hopp, Thor Edvardsen, and Kristina H. Haugaa. 2016. “Strain Echocardiography Is Related to Fibrosis and Ventricular Arrhythmias in Hypertrophic Cardiomyopathy.” *European Heart Journal - Cardiovascular Imaging* 17 (6): 613-21. doi:10.1093/ehjci/ jew005.
- Hasselberg, Nina E., Kristina H. Haugaa, Anne Bernard, Margareth P. Ribe, Erik Kongsgaard, Erwan Donal, and Thor Edvardsen. 2016. “Left Ventricular Markers of Mortality and Ventricular Arrhythmias in Heart Failure Patients with Cardiac Resynchronization Therapy.” *European Heart Journal Cardiovascular Imaging* 17 (3): 343-50. doi:10.1093/ehjci/jev173.
- Haugaa, Kristina H., Cristina Basso, Luigi P. Badano, Chiara Bucciarelli-Ducci, Nuno Cardim, Oliver Gaemperli, Maurizio Galderisi et al. 2017. “Comprehensive Multi-Modality Imaging Approach in Arrhythmogenic Cardiomyopathy—an Expert Consensus Document of the European Association of Cardiovascular Imaging.” *European Heart Journal - Cardiovascular Imaging*, jew229. doi:10.1093/ehjci/jew229.
- Haugaa, Kristina H., Björn Goebel, Thomas Dahlslett, Kathleen Meyer, Christian Jung, Alexander Lauten, Hans R. Figulla, Tudor C. Poerner, and Thor Edvardsen. 2012. “Risk Assessment of Ventricular Arrhythmias in Patients with Nonischemic Dilated Cardiomyopathy by Strain Echocardiography.” *Journal of the American Society of Echocardiography* 25 (6): 667-73. doi:10.1016/j.echo.2012.02.004.
- Haugaa, Kristina H., Bjørnar L. Grenne, Christian H. Eek, Mads Ersbøll, Nana Valeur, Jesper H. Svendsen, Anca Florian et al. 2013. “Strain Echocardiography Improves Risk Prediction of Ventricular Arrhythmias after Myocardial Infarction.” *JACC: Cardiovascular Imaging* 6 (8): 841-50. doi:10.1016/j.jcmg.2013.03.005.
- Haugaa, Kristina Hermann, Jan P. Amlie, Knut Erik Berge, Trond P. Leren, Otto A. Smiseth, and Thor Edvardsen. 2010. “Transmural Differences in Myocardial Contraction in Long-QT Syndrome: Mechanical Consequences of Ion Channel

- Dysfunction.” *Circulation* 122 (14): 1355-63. doi:10.1161/CIRCULATIONAHA.110.960377.
- Klem, Igor, Jonathan W. Weinsaft, Tristram D. Bahnson, Don Hegland, Han W. Kim, Brenda Hayes, Michele A. Parker, Robert M. Judd, and Raymond J. Kim. 2012. “Assessment of Myocardial Scarring Improves Risk Stratification in Patients Evaluated for Cardiac Defibrillator Implantation.” *Journal of the American College of Cardiology* 60 (5). Elsevier Inc.: 408-20. doi:10.1016/j.jacc.2012.02.070.
- Kocabay, Gonenc, Denisa Muraru, Diletta Peluso, Umberto Cucchini, Sorina Mihaila, Seena Padayattil-Jose, Denas Gentian, Sabino Iliceto, Dragos Vinereanu, and Luigi P Badano. 2014. “Normal Left Ventricular Mechanics by Two-Dimensional Speckle Tracking Echocardiography. Reference Values in Healthy Adults.” *Revista Española de Cardiología (English Ed.)* 67 (8): 651-58. doi:10.1016/j.rec.2013.12.009.
- Lang, Roberto M, Luigi P Badano, Victor Mor-avi, Jonathan Afilalo, Anderson Armstrong, Laura Ernande, Frank A Flachskampf et al. 2016. “Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association Of, Cardiovascular Imaging.” *European Heart Journal - Cardiovascular Imaging* 17 (4). Elsevier Inc: 412-412. doi:10.1093/ehjci/jew041.
- Marcus, Frank I., William J. McKenna, Duane Sherrill, Cristina Basso, Barbara Bauce, David A. Bluemke, Hugh Calkins et al. 2010. “Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Proposed Modification of the Task Force Criteria.” *Circulation* 121 (13): 1533-41. doi:10.1161/CIRCULATIONAHA.108.840827.
- Mignot, Aude, Erwan Donal, Amira Zaroui, Patricia Reant, Adrien Salem, Cecile Hamon, Severine Monzy, Raymond Roudaut, Gilbert Habib, and Stéphane Lafitte. 2010. “Global Longitudinal Strain as a Major Predictor of Cardiac Events in Patients with Depressed Left Ventricular Function: A Multicenter Study.” *Journal of the American Society of Echocardiography* 23 (10): 1019-24. doi:10.1016/j.echo.2010.07.019.
- Moss, Arthur J., W. Jackson Hall, David S. Cannom, James P. Daubert, Steven L. Higgins, Helmut Klein, Joseph H. Levine et al. 1996. “Improved Survival with an Implanted Defibrillator in Patients with Coronary Disease at High Risk for Ventricular Arrhythmia.” *New England Journal of Medicine* 335 (26): 1933-40. doi:10.1056/NEJM199612263352601.
- Moss, Arthur J., Wojciech Zareba, W. Jackson Hall, Helmut Klein, David J. Wilber, David S. Cannom, James P. Daubert, Steven L. Higgins, Mary W. Brown, and Mark L. Andrews. 2002. “Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction.” *New England Journal of Medicine* 346 (12): 877-83. doi:10.1056/NEJMoa013474.

- Ng, Arnold C.T., Matteo Bertini, C. Jan Willem Borleffs, Victoria Delgado, Eric Boersma, Sebastiaan R.D. Piers, Joep Thijssen et al. 2010. "Predictors of Death and Occurrence of Appropriate Implantable Defibrillator Therapies in Patients With Ischemic Cardiomyopathy." *The American Journal of Cardiology* 106 (11). Elsevier Inc.: 1566-73. doi:10.1016/j.amjcard.2010.07.029.
- Priori, Silvia G, Carina Blomström-Lundqvist, Andrea Mazzanti, Nico Blom, Martin Borggrefe, John Camm, Perry Mark Elliott et al. 2015. "2015 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death - Addenda." *European Heart Journal* 36 (41): 2793-2867. doi:10.1093/eurheartj/ehv316.
- Saberniak, Jørg, Ida S. Leren, Trine F. Haland, Jan Otto Beitnes, Einar Hopp, Rasmus Borgquist, Thor Edvardsen, and Kristina H. Haugaa. 2016. "Comparison of Patients with Early-Phase Arrhythmogenic Right Ventricular Cardiomyopathy and Right Ventricular Outflow Tract Ventricular Tachycardia." *European Heart Journal Cardiovascular Imaging*, jew014. doi:10.1093/ehjci/jew014.
- Sarvari, Sebastian I., Kristina H. Haugaa, Ole Gunnar Anfinnsen, Trond P. Leren, Otto A. Smiseth, Erik Kongsgaard, Jan P. Amlie, and Thor Edvardsen. 2011. "Right Ventricular Mechanical Dispersion Is Related to Malignant Arrhythmias: A Study of Patients with Arrhythmogenic Right Ventricular Cardiomyopathy and Subclinical Right Ventricular Dysfunction." *European Heart Journal* 32 (9): 1089-96. doi:10.1093/eurheartj/ehr069.
- Stecker, Eric C., Catherine Vickers, Justin Waltz, Carmen Socoteanu, Benjamin T. John, Ronald Mariani, John H. McAnulty, Karen Gunson, Jonathan Jui, and Sumeet S. Chugh. 2006. "Population-Based Analysis of Sudden Cardiac Death With and Without Left Ventricular Systolic Dysfunction." *Journal of the American College of Cardiology* 47 (6). Elsevier Masson SAS: 1161-66. doi:10.1016/j.jacc.2005.11.045.
- Thavendiranathan, Paaladinesh, Andrew D. Grant, Tomoko Negishi, Juan Carlos Plana, Zoran B. Popović, and Thomas H. Marwick. 2013. "Reproducibility of Echocardiographic Techniques for Sequential Assessment of Left Ventricular Ejection Fraction and Volumes." *Journal of the American College of Cardiology* 61 (1): 77-84. doi: 10.1016/j.jacc.2012.09.035.

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